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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,344,949 :
Patentee: Milton L. Hoefle and : Box:
Sylvester Klutchko : Patent
Issue Date: August 17, 1982 : Extension

REQUEST FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. 156

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. Sec. 156, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains, New Jersey, 07950, assignee of the above-identified patent by an assignment from the inventors to WARNER-LAMBERT COMPANY, recorded February 20, 1981, at Reel 3871, Frames 826-827, hereby requests an extension of the patent term of United States Patent No. 4,344,949.

The following information is submitted in accordance with 35 U.S.C. Sec. 156(d) and 37 C.F.R. 1.740, and follows the numerical format set forth in 37 C.F.R. 1.740.

(1) A complete identification of the approved product by appropriate chemical and generic name, physical structure characteristics:

The approved product is ACCUPRIL® (quinapril hydrochloride) tablet. The active ingredient in ACCUPRIL® tablet is quinapril hydrochloride. ACCUPRIL® tablet is for oral administration.

Chemically it is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, hydrochloride (S,S,S), or 2-[2-[[1-ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydroisoquinoline carboxylic acid monohydrochloride, [3S-[2[R*(R*)],3R*]] (see USAN 1991).

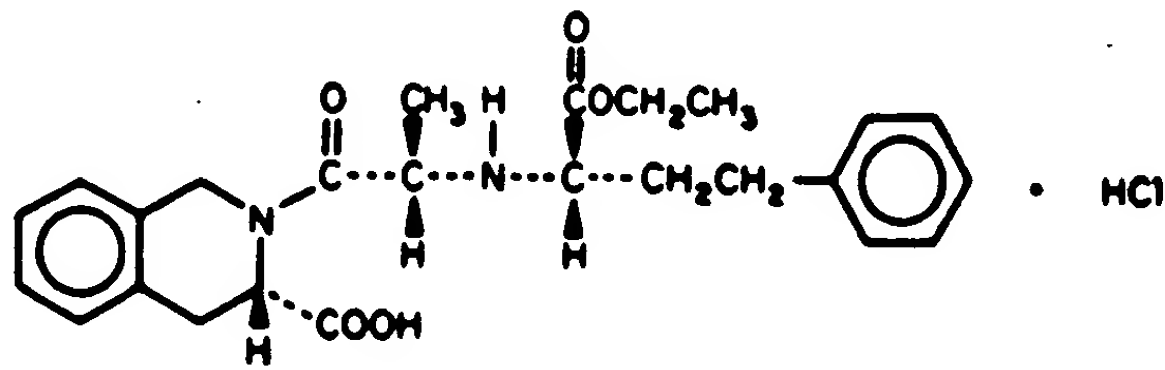
The stereochemical descriptor, [3S-[2[R*(R*)],3R*]], for the attached structure describes the single isomer of this substance for which the three chiral centers all have an "S" configuration as defined in the Cahn-Ingold-Prelog stereochemical nomenclature system. The descriptor is written following conventions used by Chemical Abstracts Service, Columbus, Ohio.

In describing the configuration of atoms in a molecule, this system uses the designation "R" or "S" to define one chiral center (known as the reference center) absolutely and then describes all other chiral centers in relation to the reference center, using relative descriptors such as cis, trans, α , β , R*, or S*. R* and S* are relative descriptors that describe centers of the same configuration as (R*), or opposite configuration from (S*), the reference center.

In the case of quinapril hydrochloride where centers exist both in the ring and in the side chain attached to the ring, the center in the ring is the reference center to which the others are related. The "3S" describes the 3 position on the isoquinoline ring as having an absolute configuration of S. The [2[R*(R*)] describes the two centers in the side chain at the 2 position as absolute configuration. The 3R* is purely conventional and refers to the 3 position in the ring because the system requires the reference center to have a relative descriptor in addition to the absolute descriptor.

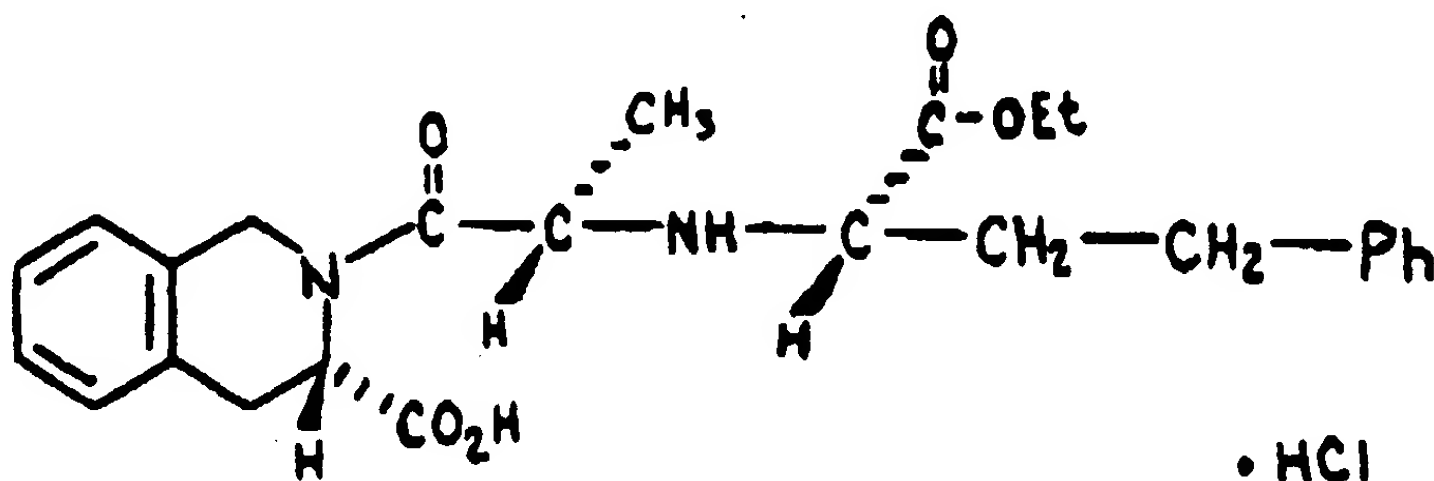
The name CI-906 hydrochloride (CI-906) is the internal name used by WARNER-LAMBERT COMPANY.

Quinapril hydrochloride has the structural formula shown by each of the following:



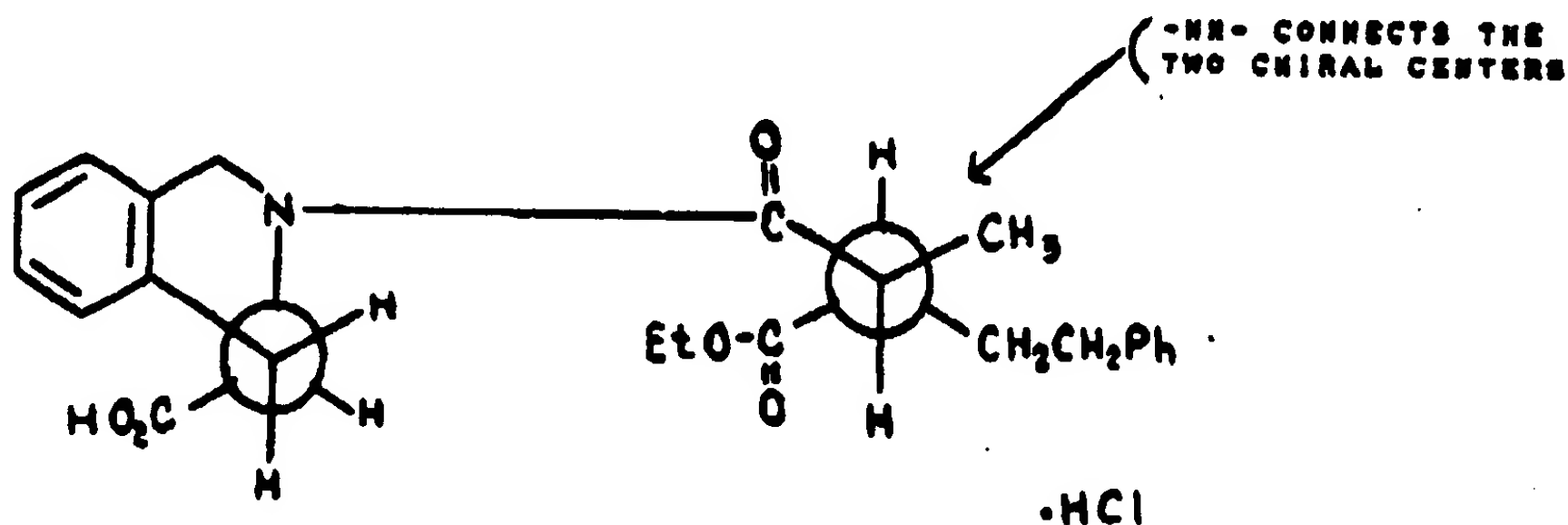
USAN

or



FLYING-WEDGE PROJECTION

or



NEWMAN PROJECTION

As noted above, ACCUPRIL® tablet is a pharmaceutical composition containing quinapril hydrochloride for oral use; see the section entitled DESCRIPTION, DOSAGE AND ADMINISTRATION in Exhibit 1 (PACKAGE INSERT) which is the Product Information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. Sec. 301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for antihypertension products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

ACCUPRIL® (quinapril hydrochloride) tablet was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to Section 505(b) of the FFDCA on November 19, 1991; see Exhibit 2 (APPROVAL LETTER).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The only active ingredient in ACCUPRIL® (quinapril hydrochloride) tablet is quinapril hydrochloride. Quinapril hydrochloride has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to Sec. 1.720(f) and an identification of the last day on which the application could be submitted.

The product was approved for commercial marketing on November 19, 1991, and the last day within the sixty day period permitted for submission of an application for extension of the patent is January 18, 1991. The date of submission of the present application is no later than January 18, 1991, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NO. 4,344,949

INVENTORS: Milton Louis Hoefle
and Sylvester Klutchko

Issue Date: August 17, 1982

Expiration Date: August 17, 1999

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,344,949 is attached as Exhibit 3 (PATENT).

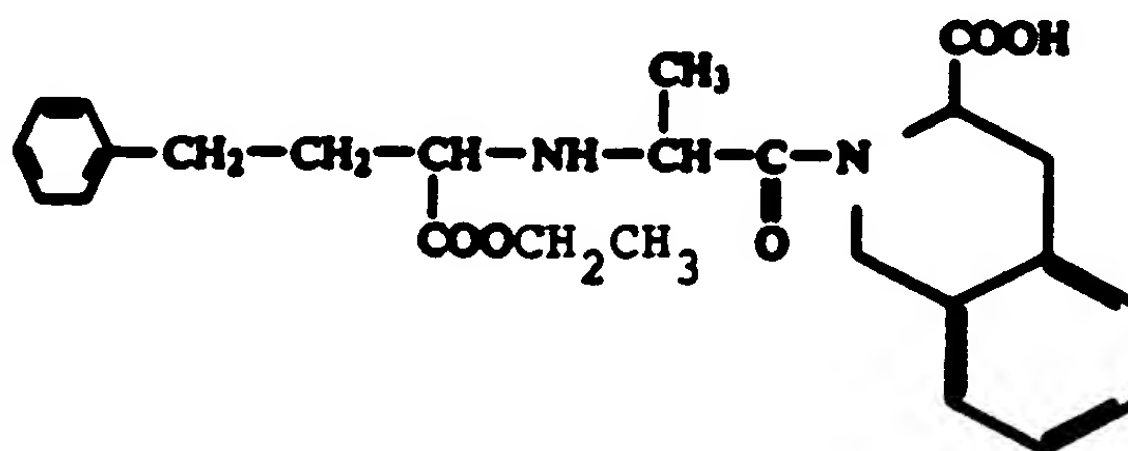
(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

No disclaimer, certificate of correction or re-examination certificate has been issued. No maintenance fee is required.

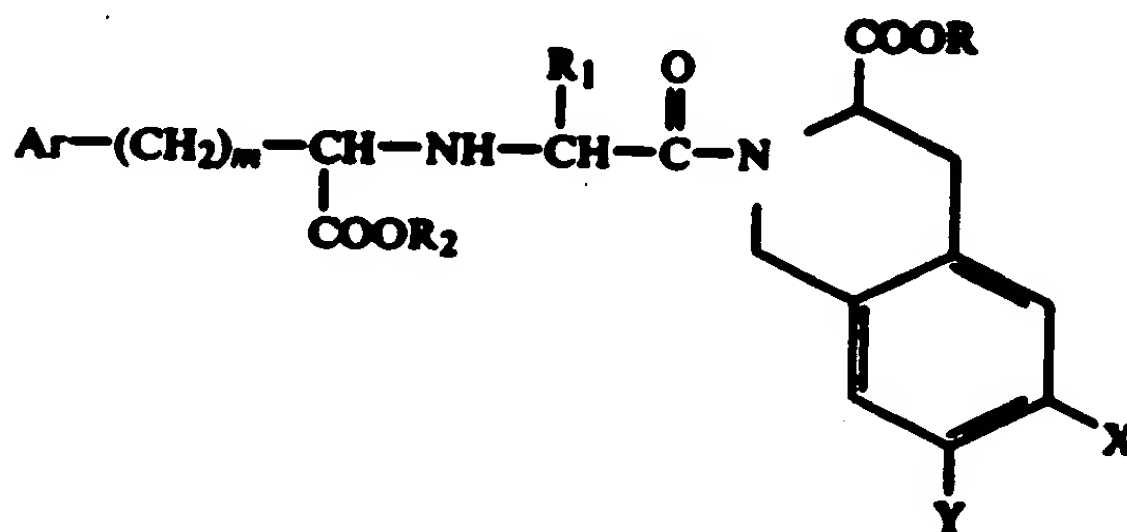
(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

The patent claims quinapril hydrochloride, the active ingredient of the approved product, ACCUPRIL® tablet, generically in claims 1, 2, and 4.

The structural formula for quinapril hydrochloride is the S,S,S, configuration of the following formula:



Structural formula of the compounds claimed in Claim 1 is as follows:

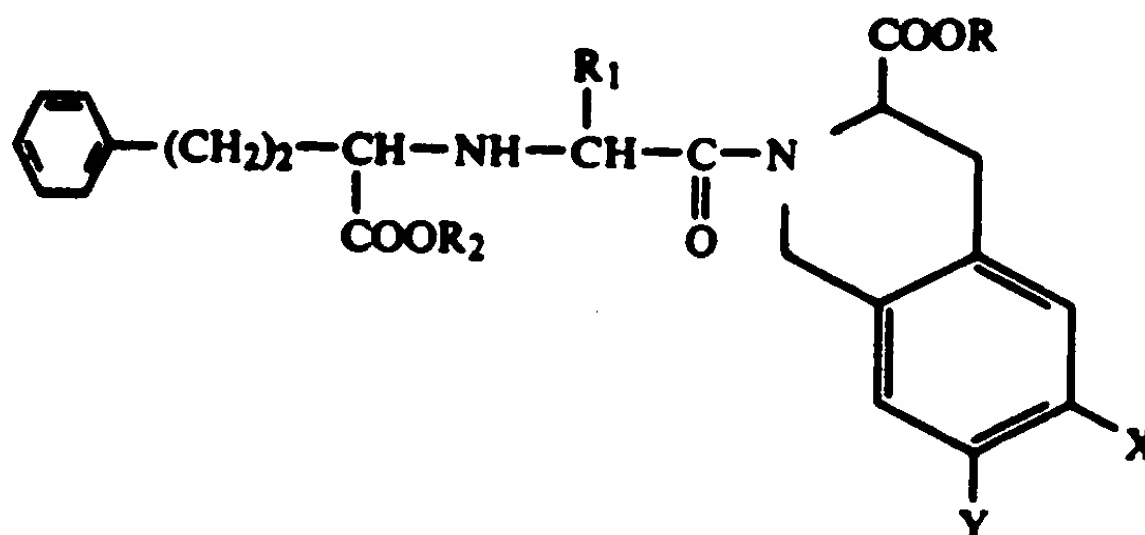


It is evident from a comparison of the two structural formulas that R, X and Y in the formula of Claim 1 of the patent must each be hydrogen, and R₁ must be methyl, R₂ must be ethyl, m must be 2 and Ar must be phenyl for the compound defined by structural formula to read on quinapril.

Claim 1 contains the required definitions of these substituents to read on quinapril.

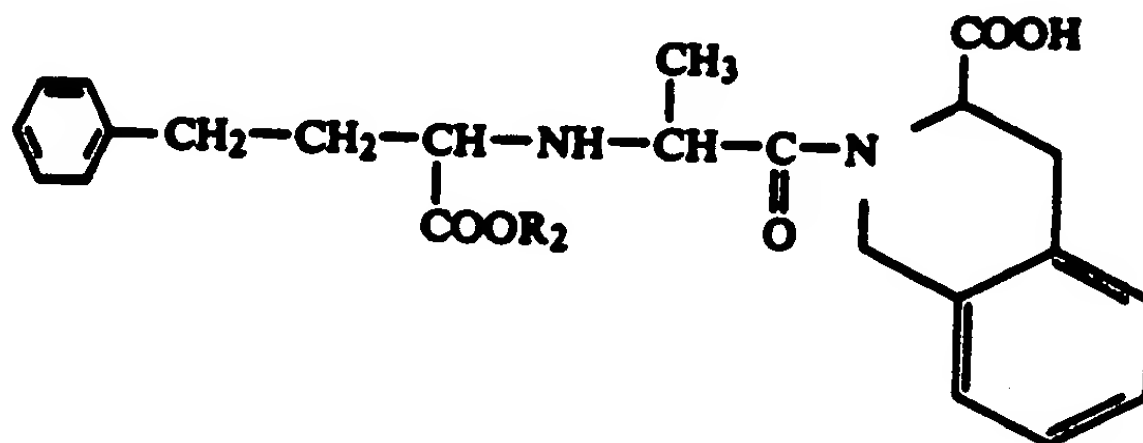
Claims 2 and 4 are also generic to quinapril.

Claim 2 contains the following structural formula:



Thus the Claim 2 formula differs from the formula of Claim 1 in that the Ar substituent is shown as phenyl, m is shown as 2, and R, R₁, R₂, X and Y are more narrowly defined but still read on quinapril.

Claim 4 contains the following structural formula:



The Claim 4 formula differs from the formula of Claim 1 in that in addition to the Ar shown as phenyl, the $(CH_2)_m$ is shown as CH_2CH_2 , R_1 is shown as CH_3 , R is shown as hydrogen, X and Y are each shown as hydrogen and R_2 is more narrowly defined but still reads on quinapril.

Claim 13 claims 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, hydrochloride (S,S,S) which is quinapril hydrochloride.

In addition, each of Claims 1, 2, 4, and 13 read on a pharmaceutically acceptable salt of quinapril which includes hydrochloride.

Claim 14 claims a pharmaceutical composition comprising 10 to 500 mg of a compound defined according to Claim 1 or a pharmaceutically acceptable salt thereof. Therefore, Claim 14 reads on all DOSAGES of the approved product, ACCUPRIL® tablet (quinapril hydrochloride).

Claim 15 is for a method of treating hypertension by administering an effective amount of a compound defined in Claim 1 or a pharmaceutically acceptable salt thereof which reads on quinapril hydrochloride. Claim 15 reads on the ADMINISTRATION of the approved product, ACCUPRIL® tablet (quinapril hydrochloride).

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. Sec. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved:

On May 17, 1982, Parke-Davis Pharmaceutical Research Division of WARNER-LAMBERT COMPANY, the patent owner, submitted to the Food and Drug Administration ("FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (hereinafter referred to as an "IND") for CI-960 hydrochloride (quinapril hydrochloride) tablet. A copy of this letter is submitted herewith as Exhibit 4 (IND SUBMISSION LETTER)

The IND was assigned number 20,336. The IND became effective on June 18, 1982, which is thirty days after receipt of the IND by the FDA; see Exhibit 5 (IND ACKNOWLEDGMENT LETTER) attached hereto. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as June 18, 1982.

On January 26, 1989, a new drug application (NDA 19,885) was initially submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) for ACCUPRIL® (quinapril hydrochloride) tablet. A copy of the cover letter of January 26, 1989, is submitted herewith as Exhibit 6 (NDA SUBMISSION LETTER).

This NDA was approved on November 19, 1991. Attached as Exhibit 2 (APPROVAL LETTER) is a copy of a letter dated November 19, 1991, from the FDA to WARNER-LAMBERT approving the NDA for the preparation ACCUPRIL® (quinapril hydrochloride) tablet.

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. 156(g)(1), November 19, 1991, is the date of the first approval of quinapril hydrochloride, which is the active ingredient in ACCUPRIL® tablet.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), WARNER-LAMBERT COMPANY submitted an IND for quinapril hydrochloride tablet on May 17, 1982, which became effective on June 18, 1982, and, in close consultation with FDA, subsequently conducted clinical studies under this IND. The studies under the IND are summarized in the attached Exhibit 7 (IND LOG) entitled "REGULATORY LIAISON AND COMPLIANCE MANAGEMENT SYSTEM CI NUMBER 906 APPLICATION NUMBER=20,336." These studies were used to support the new drug application submitted by WARNER-LAMBERT COMPANY on January 26, 1989.

Subsequent to the submission of this NDA, WARNER-LAMBERT COMPANY had numerous contacts and meetings with the FDA with respect to the application and these are summarized in the attached Exhibit 8, (NDA LOG) entitled "REGULATORY LIAISON AND COMPLIANCE INFORMATION MANAGEMENT SYSTEM CI NUMBER= 906 APPL. NUMBER= 19-885."

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension
Under 35 U.S.C. Sec. 156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. Sec. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and Section 156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here:

- (1) The term of U.S. Patent No. 4,344,949 expires on August 17, 1999. This application has, therefore, been submitted before the expiration of the patent term. In addition, there is no required

maintenance fee because the patent was filed before a maintenance fee was effected and the patent is in force.

- (2) The term of this patent has never been extended.
- (3) This application is submitted by the owner of record, WARNER-LAMBERT COMPANY, (Assignment recorded on February 20, 1981, at Reel 3871, Frames 826-827). This application is submitted in accordance with 35 U.S.C. Sec. 156(d) in that it is submitted within the sixty-day period beginning on the date, November 19, 1991, that the product received permission for marketing under the Federal Food Food, Drug and Cosmetic Act and contains the information required under 35 U.S.C. Sec. 156(d).
- (4) As evidenced by the November 19, 1991, letter from the FDA, Exhibit 2, (APPROVAL LETTER) the product was subject to a regulatory review period under Section 505(b)(1) of the FFDCA before its commercial marketing or use.
- (5) The permission for the commercial marketing of ACCUPRIL® (quinapril hydrochloride) tablet after regulatory review under Section 505(b)(1) is the first permitted commercial marketing of quinapril hydrochloride. This is confirmed by the absence of any approved new drug application under which quinapril hydrochloride could be commercially marketed prior to November 19, 1991.

- (6) No other patent has been extended for the same regulatory period for the approved product (Section 156(c)(4)).

Statement as to Length of Extension Claimed
In Accordance With 37 C.F.R. 1.775

The term of U.S. Patent No. 4,344,949 should be extended for a period of 2 years to August 17, 2001.

The period of extension is determined in accordance with 35 U.S.C. Section 156 and follows the format set forth in 37 CFR 1.775(c) and (d).

37 CFR 1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of --

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

The number of days between the effective date of the initial IND, June 18, 1982, and the initial submission of the NDA, January 26, 1989, is a period of 2414 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of the NDA, January 26, 1989, to NDA approval, November 19, 1991, is a period of 1027 days.

37 C.F.R. 1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on June 18, 1982, which were on or before August 17, 1982, the date the patent was issued, is a period of 60 days,

2414 days minus 60 days equals 2354 days,

and

the number of days in the period of the NDA, effective on January 26, 1989, which

were on or before August 17, 1982, the date the patent was issued, is a period of 0 days,

1027 days minus 0 days equals 1027 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the applicant did not act with due diligence is 0 days,

therefore,

2354 days minus 0 days equals 2354 days.

1027 days minus 0 days equals 1027 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2354 days equals 1177 days.

Thus U.S. Patent No. 4,344,949 should be entitled to an extension of 2204 days (1177 days plus 1027 days).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 2204 days to August 17, 1999, the original term of the patent (no terminal disclaimer was made), extends the term to August 29, 2005.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to November 19, 1991,
the date of approval of the application,
gives the date of November 19, 2005.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is August 29, 2005.

(5) If the original patent was issued after September 24, 1984,

This is not applicable for the patent.

(6) If the original patent was issued before September 24, 1984, and

(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--

This is not applicable for the patent.

(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--

(A) Adding 2 years to the original expiration date of the patent or earlier date set by terminal disclaimer,

Adding 2 years to August 17, 1999 equals
August 17, 2001.

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

August 17, 2001 is the earlier date.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

WARNER-LAMBERT COMPANY filed an NDA application with respect to the combination of quinapril hydrochloride plus hydrochlorothiazide tablets. The IND with respect to the tablets was assigned number 34-487 and the NDA was assigned number 20-125 which has not yet been approved. ACCUPRIL® tablet is the first quinapril hydrochloride containing product approved by the FDA.

(14) Prescribed Fee:

The prescribed fee of \$600.00 for receiving and acting on this application for extension of patent term is hereby authorized. Please charge Deposit Account No. 23-0450 in the amount of the fee above, or such greater or lesser amount of excess fees as the Commissioner determines is required by law.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Joan Thierstein
Registration No. 29,450
Patent Department
WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, Michigan 48105
Telephone: (313) 996-7190

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. 1.740.

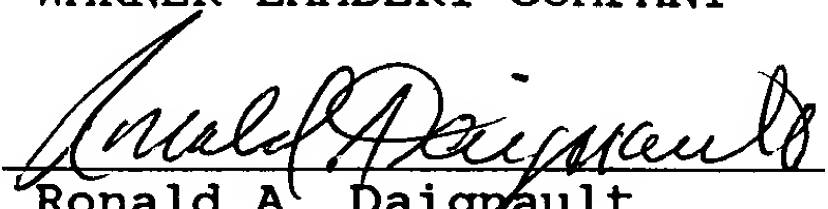
DECLARATION

The undersigned is authorized to obligate WARNER-LAMBERT COMPANY, the owner of record of U.S. Patent 4,344,949, which has applied for an extension of term of this patent, I declare that, I have reviewed and understand the contents of this application being submitted pursuant to this section; that I believe that the patent is subject to extension pursuant to 37 C.F.R. 1.710; that I believe that the length of extension claimed is fully justified under 35 U.S.C. 156 and the applicable regulations; and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,344,949.

WARNER-LAMBERT COMPANY

By:


Ronald A. Daigault

Reg. No. 25,968

Assistant Secretary

WARNER-LAMBERT COMPANY

Pharmaceutical Research Division

2800 Plymouth Road

Ann Arbor, Michigan 48105

(313) 996-7530

Date:

November 25, 1991

JT1S3943.DOC

19

CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No: _____ Date of Deposit _____

I hereby certify that this transmittal together with the application for extension of patent term under 35 U.S.C. 156 referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington D.C. 20231.

Name of Person Mailing Paper

Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent No. 4,344,949
Issued : August 17, 1982
Patentee(s) : Milton L. Hoefle and
Sylvester Klutchko
For : SUBSTITUTED ACYL DERIVATIVES OF 1,2,3,4-
TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACIDS

Attention: Charles Van Horn
BOX: PATENT TERM EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

TRANSMITTAL OF AN APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for a product approved on November 19, 1991.


- [] The application is being mailed by Express Mail under 37 CFR 1.10 and the required Certificate of Mailing appears above. The use of this certificate is intended to insure that the application will be considered as timely filed.
- [X] A prescribed fee in the amount of \$600.00 is required for the application presented.

Please charge Deposit Account No. 23-0450 in the amount of the fee above, or such greater or lesser amount of fees for the application as the Commissioner determines is required by law. This letter is submitted in triplicate.

- [X] Three working copies of the APPLICATION FOR EXTENSION OF PATENT TERM and attachments to each are provided for the convenience of the U.S. Patent and Trademark Office.

Respectfully submitted,

November 25, 1991
Date



JOAN THIERSTEIN, Attorney
Registration No. 29,450
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (313)996-7190

- Attachments:
- [X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 with Declaration and attachments thereto
 - [X] A certified duplicate original APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto
 - [X] Three working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto
 - [X] Form WL-1 (transmittal - in triplicate)

PACKAGE INSERT

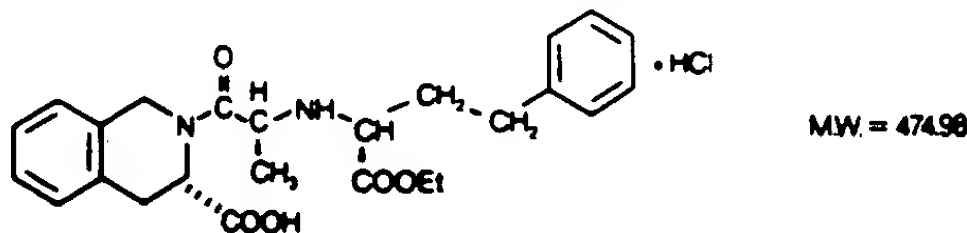
Accupril[®]

(Quinapril Hydrochloride Tablets)

DESCRIPTION

ACCUPRIL (quinapril hydrochloride) is the hydrochloride salt of quinapril, the ethyl ester of a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor, quinapril.

Quinapril hydrochloride is chemically described as [3S-[2(R)(R'), 3R']]-2-[2-[(1S)-ethoxycarbonyl]-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isquinolinecarboxylic acid, monohydrochloride. Its empirical formula is $C_{26}H_{34}N_2O_4 \cdot HCl$ and its structural formula is



Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents.

ACCUPRIL tablets contain 5 mg, 10 mg, 20 mg, or 40 mg of quinapril for oral administration. Each tablet also contains candellite wax, croscopolone, gelatin, lactose, magnesium carbonate, magnesium stearate, synthetic red iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, norepinephrine or epinephrine. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with ACCUPRIL alone resulted in mean increases in potassium of 0.07 mmol/L (see PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. ACCUPRIL was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in nonblacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

Pharmacokinetics and Metabolism: Following oral administration, peak plasma quinapril concentrations are observed within one hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is at least 80%. The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when ACCUPRIL tablets are administered during a high-fat meal. Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 35% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of ACCUPRIL, there is an effective accumulation half-life of quinaprilat of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose. Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose, and has an elimination half-life in plasma of approximately 2 hours and a prolonged terminal phase with a half-life of 25 hours. The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5-80 mg doses and 40-160 mg in multiple daily doses. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic hemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. Elimination of quinaprilat is reduced in elderly patients (≥ 65 years); this reduction is attributable to decrease in renal function (see DOSAGE AND ADMINISTRATION), and not to age itself. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

Pharmacodynamics and Clinical Effects: Single doses of 20 mg of ACCUPRIL provide over 80% inhibition of plasma ACE for 24 hours. Inhibition of the pressor response to angiotensin I is short-lived, with a 20 mg dose giving 75% inhibition for about 4 hours, 50% inhibition for about 8 hours, and 20% inhibition at 24 hours. With chronic dosing, however, there is substantial inhibition of angiotensin II levels at 24 hours by doses of 20-80 mg.

Administration of 10 to 80 mg of ACCUPRIL to patients with mild to severe hypertension results in a reduction of sitting and standing blood pressure to about the same extent with minimal effect on heart rate. Symptomatic postural hypotension is infrequent although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS). Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2 to 4 hours after dosing. During chronic therapy, most of the blood pressure lowering effect of a given dose is obtained in 1-2 weeks. In multiple-dose studies, 10-80 mg per day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5-11/3-7 mm Hg. The trough effect represents about 50% of the peak effect. While the dose-response relationship is relatively flat, doses of 40-80 mg were somewhat more effective at trough than 10-20 mg, and hence daily dosing tended to give a somewhat lower trough blood pressure than once daily dosing with the same total dose. The antihypertensive effect of ACCUPRIL continues during long-term therapy, with no evidence of loss of effectiveness.

Hemodynamic assessments in patients with hypertension indicate that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction.

Use of ACCUPRIL with a thiazide diuretic gives a blood-pressure lowering effect greater than that seen with either agent alone.

In patients with hypertension, ACCUPRIL 10-40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.

Therapeutic effects appear to be the same for elderly (≥ 65 years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

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(Quinapril Hydrochloride Tablets)

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately. The patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL, but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N=3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No teratogenic or embryotoxic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥ 25 mg/kg/day and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dose reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥ 5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician if actual syncope occurs. Patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

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Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if co-prescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on an mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on an mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL, where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials		
	Accupril (N=1563) Incidence (Discontinuance)	Placebo (N=579) Incidence (Discontinuance)
Headache	5.8 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.6)	2.8 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea and/or Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N=4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, heart failure, hypertension, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances

Gastrointestinal: dry mouth or throat, constipation, gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests

Nervous/Psychiatric: somnolence, vertigo, syncope, nervousness, depression

Integumentary: increased sweating, pruritus, exfoliative dermatitis, photosensitivity reaction

Urogenital: acute renal failure

Other: *embryopia, pharyngitis, sinusitis, bronchitis, agranulocytosis, thrombocytopenia*

Angioedema

Angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS.)

Hypertension: (See PRECAUTIONS.)

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Creatinine and Blood Urea Nitrogen: Increases (≥ 1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone; increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

OVERDOSAGE

No data are available with respect to overdosage in humans. Doses of 1440 to 4280 mg/kg of quinapril cause significant mortality in mice and rats.

The most likely clinical manifestation would be symptoms attributable to severe hypotension.

Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdosage.

No data are available to suggest physiological maneuvers (eg, maneuvers to change pH of the urine) that might accelerate elimination of quinapril and its metabolites.

Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of quinapril overdosage, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of quinapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat quinapril overdosage by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Monotherapy: The recommended initial dosage of ACCUPRIL in patients not on diuretics is 10 mg once daily. Dosage should be adjusted according to blood pressure response measured at peak (2-6 hours after dosing) and trough (predosing). Generally, dosage adjustments should be made at intervals of at least 2 weeks. Most patients have required dosages of 20, 40, or 80 mg/day, given as a single dose or in 2 equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice daily administration may be warranted. In general, doses of 40-80 mg and divided doses give a somewhat greater effect at the end of the dosing interval.

Concomitant Diuretics: If blood pressure is not adequately controlled with ACCUPRIL monotherapy, a diuretic may be added. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ACCUPRIL. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2 to 3 days prior to beginning therapy with ACCUPRIL (see WARNINGS). Then, if blood pressure is not controlled with ACCUPRIL alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg ACCUPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized.

The dosage should subsequently be titrated (as described above) to the optimal response (see WARNINGS, PRECAUTIONS, and Drug Interactions).

Renal Impairment: Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. Recommended starting doses, based on clinical and pharmacokinetic data from patients with renal impairment, are as follows:

Creatinine Clearance	Maximum Recommended Initial Dose
> 60 mL/min	10 mg
30-60 mL/min	5 mg
10-30 mL/min	2.5 mg
< 10 mL/min	Insufficient data for dosage recommendation

Patients should subsequently have their dosage titrated (as described above) to the optimal response. **Elderly (≥ 65 years):** The recommended initial dosage of ACCUPRIL in elderly patients is 10 mg given once daily followed by titration (as described above) to the optimal response.

HOW SUPPLIED

ACCUPRIL tablets are supplied as follows:

5-mg tablets: brown, film-coated, elliptical, scored tablets, coded "PD 527" on one side and "5" on the other.

N0071-0527-23 bottles of 90 tablets

10-mg tablets: brown, film-coated, triangular, scored tablets, coded "PD 530" on one side and "10" on the other.

N0071-0530-23 bottles of 90 tablets

N0071-0530-40 10 x 10 unit dose blisters

20-mg tablets: brown, film-coated, round, scored tablets, coded "PD 532" on one side and "20" on the other.

N0071-0532-23 bottles of 90 tablets

N0071-0532-40 10 x 10 unit dose blisters

40-mg tablets: brown, film-coated, elliptical, scored tablets, coded "PD 535" on one side and "40" on the other.

N0071-0535-23 bottles of 90 tablets

N0071-0535-40 10 x 10 unit dose blisters

Dispense in well-closed containers as defined in the USP.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).

Caution—Federal law prohibits dispensing without prescription.

Issued August 1991

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Morris Plains, NJ 07950 USA

Accupril
0527FA001

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 19-885

Food and Drug Administration
Rockville MD 20857

Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D.
2808 Plymouth Road
Ann Arbor, MI 48106-1047

NOV 19 1991

Dear Dr. Martin:

Please refer to your January 26, 1989 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Accupril (quinapril hydrochloride) 5, 10, 20, and 40 mg Tablets.

We also acknowledge receipt of your amendments and correspondence dated May 23 and 24, August 20, 21, 22, 26 (two), 29 and 30, September 4, 9, and 13, October 2 and 18 (two) and November 4, 1991.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted September 9, 1991 (package insert) and August 26, September 9 and 16, and October 18, 1991 (carton and container labels). Accordingly, the application is approved effective on the date of this letter.

In addition, we are reviewing the proposed advertising campaign that was submitted on August 26 and October 2, 1991. We note that in your August 30, 1991 conversation with Ms. Kathleen Bongiovanni, you agreed to meet with the Division of Drug Marketing, Advertising, and Communications to discuss your campaign prior to the marketing of Accupril Tablets.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.60 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PATENT

[54] SUBSTITUTED ACYL DERIVATIVES OF
1,2,3,4-TETRAHYDROISOQUINOLINE-3-
CARBOXYLIC ACIDS

[75] Inventors: Milton L. Hoefle; Sylvester Klutchko,
both of Ann Arbor, Mich.

[73] Assignee: Warner-Lambert Company, Morris
Plains, N.J.

[21] Appl. No.: 236,397

[22] Filed: Feb. 20, 1981

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 193,767, Oct. 3, 1980,
abandoned.

[51] Int. Cl.³ A61K 31/47; C07D 217/16;
C07D 491/048

[52] U.S. Cl. 424/258; 546/90;
546/141; 546/142; 546/147

[58] Field of Search 546/141, 90, 142, 147;
424/258

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Primary Examiner—Donald G. Daus

Assistant Examiner—James H. Turnipseed

Attorney, Agent, or Firm—Walter Patton

[57] ABSTRACT

Substituted acyl derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids and the pharmaceutically acceptable salts thereof are produced by coupling a suitably substituted 1,2,3,4-tetrahydroisoquinoline with a suitably substituted amino acid and when desired hydrolyzing or removing protecting groups of the resulting product. The compounds of the invention, their salts and pharmaceutical compositions thereof are useful as antihypertensive agents.

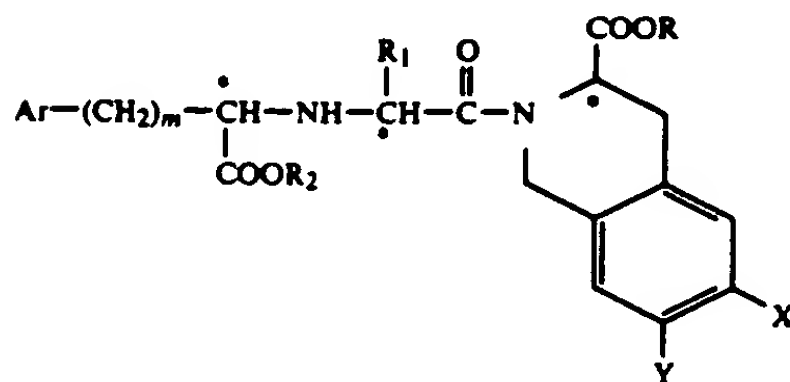
15 Claims, No Drawings

SUBSTITUTED ACYL DERIVATIVES OF 1,2,3,4-TETRAHYDROISOQUINOLINE-3-CAR- BOXYLIC ACIDS

This is a continuation-in-part of copending United States Patent application U.S. Ser. No. 193,767, filed Oct. 3, 1980, now abandoned.

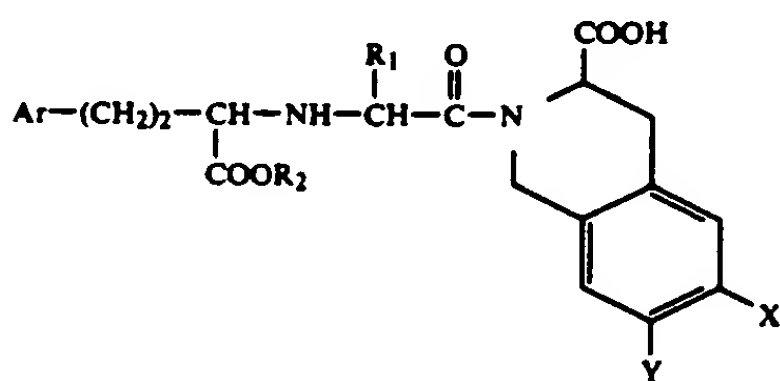
SUMMARY AND DETAILED DESCRIPTION

The invention relates to substituted acyl derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid compounds having the formula



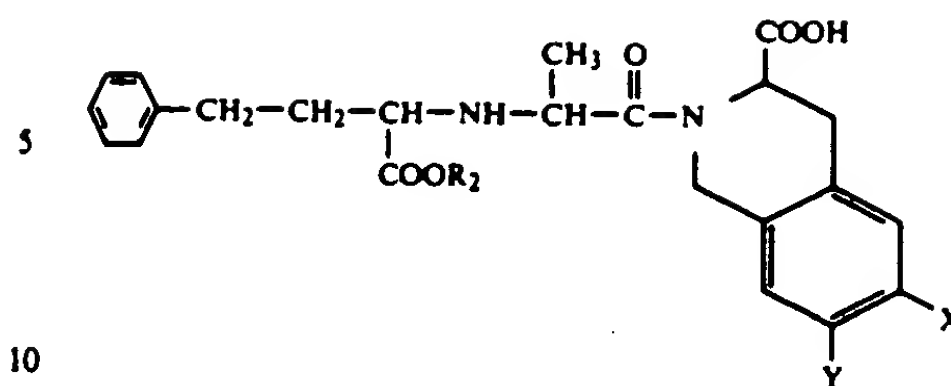
where R is hydrogen, lower alkyl or aralkyl; R₁ is hydrogen, lower alkyl, or benzyl; R₂ is hydrogen or lower alkyl, and Ar is phenyl or phenyl substituted with 1 or 2 substituents selected from the group consisting of fluorine, chlorine, bromine, lower alkyl, lower alkoxy, hydroxy or amino; X and Y are independently hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, or X and Y together are methylenedioxy; m is 0 to 3; and the pharmaceutically acceptable acid salts thereof.

Preferred compounds of the invention are acylated 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids having the formula



where R₁ is hydrogen or lower alkyl containing 1 to 3 carbon atoms, R₂ is hydrogen or lower alkyl containing 1 to 3 carbon atoms and Ar is phenyl, and phenyl substituted in the para position by fluorine, chlorine, bromine, methyl, hydroxy, methoxy or amino, X and Y are as defined above; and pharmaceutically acceptable acid salts thereof.

Further preferred compounds of the invention are acylated 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids having the formula



where R₂ is hydrogen or lower alkyl containing 1 to 3 carbon atoms X and Y are independently hydrogen or lower alkoxy and pharmaceutically acceptable acid salts thereof; and specifically the compounds designated 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid; 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid; 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid; 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid; and pharmaceutically acceptable acid salts thereof.

The terms "lower alkyl" and "lower alkoxy" are intended to mean a straight or branched alkyl group of from one to four carbon atoms.

The compounds of the invention of formula I have asymmetric carbon atoms indicated by asterisks. The 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid used in this invention has the L (S) configuration. This configuration has been shown to be required for biological activity, and thus active compounds of the invention are derived from either L(-) or DL-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids.

Optical and diastereo isomers arising from the chirality at the centers marked with an asterisk in formula I and racemates and mixtures thereof are within the scope of this invention. The S configuration at these centers is preferred.

The compounds of the invention may exist in anhydrous form as well as in solvated, including hydrated forms. In general, the hydrated forms and the solvated forms with pharmaceutically acceptable solvents are equivalent to the anhydrous or unsolvated form for the purposes of the invention.

The compounds of the invention of formula I may be prepared from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid by first protecting the carboxylic acid group, preferably as an ester, e.g., with a lower alkyl, benzyl or trimethylsilyl group. The protected carboxylic acid compound is coupled to an N-protected amino acid, e.g., glycine or L-alanine, protected on nitrogen with t-butyloxycarbonyl or benzyloxycarbonyl. The coupling is carried out by any of a variety of standard peptide coupling techniques as disclosed, for example, in "The Peptides. Analysis, Synthesis, Biology, Vol. 1 Major Methods of Peptide Bond Formation, Part A", ed. E. Gross, J. Meierhofer, Academic Press N.Y. (1979). An especially useful method involves the use of a dehydrating agent, such as dicyclohexylcarbodiimide alone or in the presence of reagents forming reactive esters, e.g., 1-hydroxybenztriazole, in suitable aprotic solvents such as dimethylformamide, acetonitrile, tetrahydrofuran or chlorinated hydrocarbons. This gives the intermediate (N-protected-2-aminoacyl)-1,2,3,4-tet-

rahydroisoquinoline-3-carboxylic acid esters. These may then be either partially or totally deblocked depending on the protecting groups chosen, using anhydrous acids, e.g., hydrochloric acid in acetic acid or trifluoroacetic acid in methylene chloride, or hydrogen gas and a catalyst to give the intermediate dipeptide either in free form or protected as an ester.

The compounds of the invention of formula I may then be prepared by reacting the intermediate dipeptide or its ester derivative with α -keto-4-substituted phenylbutyric acid or its lower alkyl ester derivatives under dehydrating and reducing conditions. Preferred dehydrating agents include molecular sieves in aprotic solvents and preferred reducing agents include sodium cyanoborohydride or hydrogen gas with a catalyst.

Alternatively, the dipeptide or its ester derivative may be reacted with an α -halo-4-substituted phenylbutyric acid or its ester in the presence of a suitable basic reagent, such as triethylamine or alkali carbonates or bicarbonates, in a solvent, to give the compounds of the invention of formula I. Ester protected products may be hydrolyzed under basic or acidic reaction conditions to free acid derivatives, or, in the case of benzyl esters, catalytic hydrogenolysis may be preferred.

Alternately, compounds of the invention of formula I may be prepared in a different manner. This consists of applying either of the two methods described above for the attachment of the 2-(4-phenylbutyric acid) moiety to the protected dipeptide, first to glycine or L-alanine, which may be protected as an ester, to give N-[2-(4-phenylbutyric acid)]-substituted glycine or L-alanine derivative.

After selective deblocking of the acid moiety on the glycine or alanine portion of the product, the resulting monoacid may be coupled, either directly or subsequent to suitable blocking of the amino group, via standard peptide coupling procedures to the 1,2,3,4-tetrahydro-3-isoquinoline carboxylate, protected as an ester. Selective or complete removal of the ester groups and any amine protecting groups yield the compounds of formula I.

The products are obtained typically as a mixture of diastereoisomers which can be separated by standard methods of fractional crystallization or chromatography.

The compounds of this invention form acid salts with various inorganic and organic acids which are also within the scope of the invention. The pharmaceutically acceptable acid addition salts of the compounds of the present invention may be prepared by conventional reactions by reacting the free amino acid or amino ester form of the product with one or more equivalents of the appropriate acid providing the desired anion in a solvent or medium in which the salt is insoluble, or in water and removing the water by freeze drying. The salts of strong acids are preferred. As exemplary, but not limiting, of pharmaceutically acceptable acid salts are the salts of hydrochloric, hydrobromic, sulfuric, nitric, acetic, fumaric, malic, maleic and citric acids.

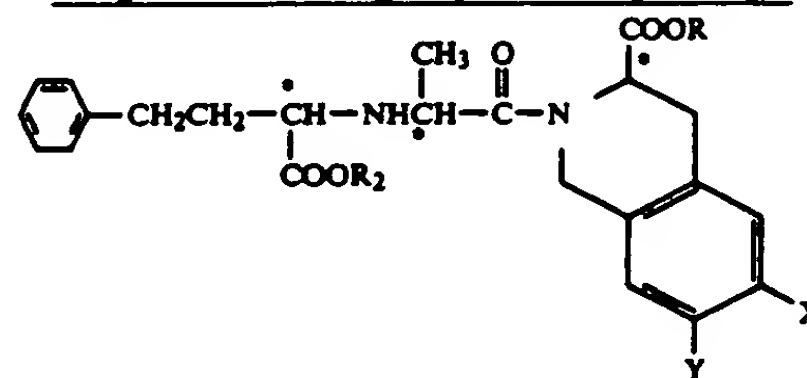
The action of the enzyme renin on angiotensinogen, a pseudoglobulin in blood plasma, produces the decapeptide angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II. The latter is an active pressor substance which has been implicated as the causative agent in various forms of hypertension in various mammalian species, e.g., rats and dogs. The compounds of this invention intervene in the renin->angiotensin I->angio-

tensin II sequence by inhibiting angiotensin I converting enzyme and reducing or eliminating the formation of the pressor substance angiotensin II, and therefore are useful in reducing or relieving hypertension. Thus by the administration of a composition containing one or a combination of compounds of formula I or pharmaceutically acceptable salts thereof, hypertension in the species of mammal suffering therefrom is alleviated. A single dose, or preferably two to four divided daily doses, provided on a basis of about 0.1 to 100 mg per kilogram per day, preferably about 1 to 50 mg per kilogram per day, is appropriate to reduce blood pressure. The substance is preferably administered orally, but parenteral routes such as subcutaneously, intramuscularly, intravenously or intraperitoneally can also be employed.

In vitro ACE Assay: Angiotensin converting enzyme (ACE) inhibitory activity was determined by assaying guinea pig serum ACE in the presence and absence of the test compound. ACE from guinea pig serum and the test compounds were preincubated for 10 minutes before the addition of the labelled substrate ^3H -hippuryl-glycyl-glycine. After a 60 minute incubation of 37°C , the reaction was stopped by the addition of 0.1 N HCl. ACE cleaves the hippuryl-glycyl bond to form the dipeptide glycyl-glycine and ^3H -hippuric acid. The ^3H -hippuric acid was then extracted with ethyl acetate and the ACE activity of a given sample calculated as the amount of ^3H -hippuric acid generated.

TABLE

Acyl Derivatives of
1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids
(S,S,S configuration) and their In-Vitro
Angiotensin-Converting Enzyme Inhibitory Activity



R	R ₂	X	Y	Optical Rotation [α] _D ²³	ACE I Activity (in vitro) IC ₅₀ Molar Conc.
H	Et	H	H	+10.9° (1.0% EtOH) ⁺	8.3 × 10 ⁻⁹
H	Et	OCH ₃	OCH ₃	+31.6° (1.0% EtOH) ⁺	5.6 × 10 ⁻⁹
H	H	H	H	+14.5° (1.0% MeOH) ⁺	2.8 × 10 ⁻⁹
H	H	OCH ₃	OCH ₃	+37.8° (1.0% MeOH) ⁺	3.4 × 10 ⁻⁹
PhCH ₂	Et	H	H	-11.7° (1.0% MeOH) [#]	2.0 × 10 ⁻⁶
t-Bu	Et	H	H	+6.4° (2.0% MeOH) [#]	3.2 × 10 ⁻⁶
PhCH ₂	Et	OCH ₃	OCH ₃	+3.4° (1.0% EtOH) [#]	3.0 × 10 ⁻⁷

⁺ Hydrochloride Salt

[#] Maleate Salt

The compounds of the invention can be utilized to achieve the reduction of blood pressure by formulating in compositions such as tablets, capsules or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. About 10 to 500 mg of a compound or mixture of compounds of formula I or physiologically acceptable salt thereof is compounded

with a physiologically acceptable vehicle, carrier, excipient binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The invention is illustrated by the following examples.

EXAMPLE 1

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Hydrochloride, Hydrate (S,S,S).

A quantity of 0.0079 mole of the hydrochloride of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, phenylmethyl ester (S,S,S) dissolved in 100 ml of tetrahydrofuran was catalytically debenzylated with hydrogen and 0.5 g of 20% Pd/carbon at low pressure. The catalyst was filtered off and the product was precipitated as a relatively nonhydroscopic solid by the addition of a 10 fold quantity of ether; wt 3.7 g (88%); mp 120°-140° C.; tlc (20% MeOH-CHCl₃/SiO₂) one spot, R_f 0.5-0.7; [α]_D²³ = +31.6° (1.05% EtOH).

Anal. Calc'd for C₂₇H₃₄N₂O₇·HCl·H₂O: C, 58.63; H, 6.74; N, 5.07; Found: C, 58.59; H, 6.38; N, 5.06.

The noncrystalline diester hydrochloride starting material used above was prepared by treatment of 5.54 g (0.0079 mole) of the maleate salt (prepared by the process of Example 5) with excess saturated sodium bicarbonate, extraction of the free base into 50% ethylethyl acetate, treatment of this solution with excess hydrogen chloride and concentration at reduced pressure.

EXAMPLE 2

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, Hydrochloride, Hydrate, (S,S,S).

Procedure A: Debenzylolation procedure.

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, phenylmethyl ester, maleate, (S,S,S) (prepared by the procedure of Example 6) was catalytically debenzylated by the procedure set forth in Example 1 to yield the product; mp 105°-120° C.; yield, 56%; tlc (20% MeOH-CHCl₃/SiO₂) one spot R_f 0.5-0.6; [α]_D²³ = +10.9° (1.03% EtOH).

Anal. Calc'd. for C₂₅H₃₀N₂O₅·HCl·H₂O: C, 60.90; H, 6.75; N, 5.68; Found: C, 61.00; H, 6.37; N, 5.59.

Procedure B: Via cleavage of 1,1-dimethylethyl ester.

A quantity of 100 g of trifluoroacetic acid was added to 11.6 g (0.023 mole) of 2-[2-[[1-ethoxycarbonyl]-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester (S,S,S) (prepared by the procedure of Example 7). The mixture was stirred for one hour at room temperature. Most of the trifluoroacetic acid was removed on the rotary evaporator and the remaining traces were removed by the successive additions and removal by rotary evaporation of 2 × 50 ml of THF. The residual oil was dissolved in about 400 ml of dry ether and the hydrochloride was precipitated by addition of a solution of 1.0 g (excess) of dry hydrogen chloride dissolved in 20 ml of dry ether. After filtration and washing with dry ether, the filter cake was dissolved in about 250 ml of water. This solution was filtered through celite and freeze-dried to obtain the product as a partial hydrate; 10.0 g (90%); mp 113°-120° C.

Anal. Calc'd. for C₂₅H₃₀N₂O₅·HCl· $\frac{1}{2}$ H₂O: C, 61.55; H, 6.70; N, 5.74; Found: C, 61.51; H, 6.49; N, 5.70.

EXAMPLE 3

2-[2-[[1-Carboxy-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Hydrochloride, Hydrate (S,S,S).

A solution of 0.553 g (0.001 mole) of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) (prepared by the process of Example 1) in 4 ml (0.004 mole) of 1 N sodium hydroxide and 4 ml of methanol was allowed to stand at room temperature for 20 hours. The reaction solution was added to 5 ml of 1 N hydrochloric acid and concentrated at reduced pressure. The last amounts of water were removed by two successive additions and removal at reduced pressure of 25 ml portions of ethanol. The organic portion of the residue was dissolved in 0.5 ml of methanol. Chloroform (30 ml) was added and the solution was dried over sodium sulfate, charcoaled, filtered, and concentrated to give 0.45 g product. This amorphous material was dissolved in 20 ml of tetrahydrofuran and 100 ml of ether was added to precipitate a near white solid product; wt 0.4 g; mp 145°-170° C.; yield, 80%; tlc (20% MeOH-CHCl₃/SiO₂) R_f 0.1; [α]_D²³ = +37.8° (1.09% MeOH).

Anal. Calc'd for C₂₅H₃₀N₂O₇·HCl·H₂O: C, 57.19; H, 6.34; N, 5.34; Found: C, 57.17; H, 6.10; N, 5.51.

EXAMPLE 4

2-[2-[(1-Carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, Hydrochloride, Hemihydrate (S,S,S).

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) was treated by the procedure set forth in Example 3 to yield the product; mp 140°-170° C.; yield, 39%; $[\alpha]_D^{23} = +14.5^\circ$ (1.08% MeOH).

Anal. Calc'd for $C_{23}H_{26}N_2O_5 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 60.59; H, 5.97; N, 6.15; Cl, 7.77; Found: C, 60.68; H, 6.04; N, 5.89; Cl, 7.04.

EXAMPLE 5

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Maleate (S,S,S).

A stirred solution of 5.0 g (0.0158 mole) of ethyl α -[(1-carboxyethyl)amino]benzenebutanoate hydrochloride (S,S) (prepared by the process of Example 8) in 200 ml of methylene chloride was treated successively with 1.60 g (0.0158 mole) of triethylamine, 2.14 g (0.0158 mole) of 1-hydroxybenzotriazole, 5.16 g (0.0158 mole) of 1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, phenylmethyl ester free base (S-form) (prepared by the process of Example 9); and then with 3.26 g (0.0158 mole) of dicyclohexylcarbodiimide in 10 ml of methylene dichloride. Dicyclohexylurea gradually separated. The mixture was allowed to stand at room temperature overnight. Hexane (300 ml) was added and the urea was filtered. The filtrate was washed with 250 ml of saturated sodium bicarbonate, dried over sodium sulfate and concentrated to remove solvent. The viscous residue was triturated with 50 ml of ether and filtered to remove insolubles. The filtrate was concentrated to give 9.2 g (99%) of crude base.

Preparation of maleate salt: A solution of 9.0 g (0.015 mole) of the above crude base in 50 ml of ethyl acetate was treated with a warm (40° C.) solution of 1.86 g (0.016 mole) of maleic acid in 50 ml of ethyl acetate. White crystals separated; wt 7.2 g (65%); mp 139°-141° C.; tlc of base (generated with aq. sodium bicarbonate treatment of the salt and ethyl acetate extraction) showed one spot, Rf 0.7 (EtOAc/SiO₂). Recrystallization from ethyl acetate gave pure material of the same mp; $[\alpha]_D^{23} = +3.4^\circ$ (1.05% EtOH).

Anal. Calc'd for $C_{34}H_{40}N_2O_7 \cdot C_4H_4O_4$: C, 64.74; H, 6.29; N, 3.98; Found: C, 64.48; H, 6.30; N, 3.99.

EXAMPLE 6

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Maleate (S,S,S).

Ethyl α -[(1-carboxyethyl)amino]benzenebutanoate hydrochloride (S,S) (prepared by the process of Example 8) was coupled with 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, phenylmethyl ester free base (S-form) (prepared by the process of Example 10) by the same procedure used in Example 5; yield, 61%; mp 151°-153° C. (recrystallized from ethyl acetate); tlc of base showed one spot, Rf 0.8 (EtOAc/SiO₂); $[\alpha]_D^{23} = -11.7^\circ$ (1.0% MeOH).

Anal. Calc'd for $C_{32}H_{36}N_2O_5 \cdot C_4H_4O_4$: C, 67.07; H, 6.25; N, 4.35; Found: C, 66.58; H, 6.09; N, 4.25.

EXAMPLE 7

2-[2-[[1-Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid, 1,1-Dimethylethyl Ester (S,S,S).

A mixture of 8.38 g (0.03 mole) of ethyl α -[(1-carboxyethyl)amino]benzenebutanoate (free amino acid) (S,S) (prepared by the process of Example 8), 8.09 g (0.03 mole) of 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester hydrochloride (S-form) (prepared by the process of Example 11), 4.05 g (0.03 mole) of 1-hydroxybenzotriazole and 250 ml of THF was cooled in an ice bath to 3°-5° C. With stirring, 3.04 g (0.03 mole) of triethylamine was added, then a solution of 6.92 g (0.0335 mole) of dicyclohexylcarbodiimide in 30 ml of THF was dropped in slowly over 20 minutes. The reaction mixture was stirred at 3°-5° C. for one hour. The ice bath was removed, and the reaction mixture stirred an additional 3 hours. The separated mixture of triethylamine hydrochloride and dicyclohexylurea was removed by filtration and washed with THF. The filtrate was evaporated on the rotary evaporation to remove all volatiles. The resulting gum was dissolved in about 300 ml of ethyl acetate. After filtration through celite the ethyl acetate solution was extracted 2 times with 100 ml of saturated sodium bicarbonate solution, once with 75 ml of 2 N citric acid solution, once with 100 ml of saturated sodium bicarbonate solution and once with 100 ml of saturated sodium chloride solution. After drying with anhydrous MgSO₄ and filtration, the ethyl acetate was removed on the rotary evaporator to yield 16.9 g of a light brown gum. This gum was dissolved in 350 ml of boiling hexane and decanted through celite. The hexane solution was cooled in ice, seeded and stirred until crystallization was well established. The product was filtered, washed with cold hexane and dried; wt 11.6 g (78%); mp 68.5°-71° C.; $[\alpha]_D^{23} = -12.2^\circ$ (2% MeOH). Pure material had mp 71°-72° C.; $[\alpha]_D^{23} = -12.6^\circ$ (2% MeOH). The maleate salt had mp 127.5°-128.5° C.; $[\alpha]_D^{23} = +46.4^\circ$ (2% MeOH).

EXAMPLE 8

Ethyl α -[(1-Carboxyethyl)amino]benzenebutanoate Hydrochloride (S,S).

A solution of 2.0 g of t-butyl alanine (S-form) and 3.78 g of ethyl 2-bromo-4-phenylbutanoate in 25 ml of dimethylformamide was treated with 1.8 ml of triethylamine and the solution was heated at 70° C. for 18 hours. The solvent was removed at reduced pressure and the residue was mixed with water and extracted with ethyl ether. The organic layer was washed with water and dried over magnesium sulfate. Concentration of the solvent at reduced pressure gave the oily t-butyl ester of the intermediate which was found to be sufficiently pure by gas liquid chromatography for further use.

A solution of 143.7 g of this t-butyl ester in 630 ml of trifluoroacetic acid was stirred at room temperature for one hour. The solvent was removed at reduced pressure and the residue was dissolved in ethyl ether and again evaporated. This operation was repeated. Then the ether solution was treated dropwise with a solution of hydrogen chloride gas in ethyl ether until precipitation ceased. The solid, collected by filtration, was a mixture

of diastereoisomers, mp 153°-165° C., $[\alpha]_{D23} = +3.6^\circ$ (1% MeOH).

In order to separate the preferred, S, S isomer, a suspension of 10.0 g of the mixture in 200 ml of methylene chloride was stirred at room temperature for five minutes and filtered; the solid was washed with additional methylene chloride and finally ether. The solid material, mp 202°-208° C. (dec.), $[\alpha]_{D23} = -29.3^\circ$ (1% MeOH) was the less preferred diastereoisomer having the R, S configuration (S referring to the portion derived from L-alanine). The preferred S, S diastereoisomer was recovered from the filtrate after concentration and trituration of the residue with ether; mp 137°-139° C.; $[\alpha]_{D23} = +31.3^\circ$ (1% MeOH).

The free amino acid (S,S-form) was prepared by treatment of an aqueous solution of the hydrochloride with saturated sodium acetate. The product was filtered, washed efficiently with cold water and recrystallized from ethyl acetate; mp 149°-151° C.; $[\alpha]_{D23} = +29.7^\circ$

(1% 0.1 N HCl).

EXAMPLE 9

1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Hydrochloride (S-form).

A mixture of 1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride (S-form) and 600 ml of benzyl alcohol was saturated with hydrogen chloride gas. The temperature rose to 45° C. The mixture was stirred at room temperature for three days. A relatively small amount of solid was filtered off and the filtrate was treated with ca 2-liters of ether to precipitate crude product; wt 37.5 g; yield, 83%. Purification was effected by treatment with excess saturated sodium bicarbonate, extraction of base into ethyl acetate and precipitation of hydrochloride salt with HCl gas. Recrystallization from methanol-ether gave pure product; mp 255°-260° C.; $[\alpha]_{D23} = -81.3^\circ$ (1.0% MeOH); tlc (20% MeOH-CHCl₃SiO₂) one spot Rf 0.8.

Anal. Calc'd for C₁₉H₂₁NO₄.HCl: C, 62.72; H, 6.10; N, 3.85; Found: C, 62.54; H, 5.99; N, 4.00.

EXAMPLE 10

1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid, Phenylmethyl Ester, Hydrochloride (S-form).

Benzyl alcohol, 750 ml, was treated with 150 g of commercial polyphosphoric acid and warmed and stirred at 90° C. to obtain a homogeneous mixture. Solid 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (S-form) 165.2 g was added. The mixture was stirred 4 hours at 95°-105° C. and then allowed to stand at room temperature for 18 hours. A solution of 18.5 g gaseous hydrochloric acid in 2.5 l of anhydrous ether was added, and the product separated slowly on cooling overnight. Filtration gave the crude benzyl 1,2,3,4-tetrahydro-3-isoquinoline carboxylate hydrochloride. This was purified by recrystallization from ethanol twice to give material with mp 190.5°-191° C.; $[\alpha]_{D23} = -83.3^\circ$ (1% 1:1 methanol/1 N hydrochloric acid).

EXAMPLE 11

1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid, 1,1-Dimethylethyl Ester Hydrochloride (S-form).

This compound was prepared by passing 447 g of isobutylene into a 0° C. solution of 63.5 g of 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (S-form) in 650

ml of dry dioxane and 65 ml of concentrated sulfuric acid under nitrogen. The reaction vessel was sealed and shaken for 17 hours at room temperature. The reaction vessel was vented and the mixture was poured into 25 l of cold 2 N sodium hydroxide. The produce is extracted into ether. The ether solution was washed with water, dried, and concentrated to about 500 ml. This was treated with excess 6 N isopropanolic hydrochloric acid to precipitate the product, which was collected by filtration. A sample purified by recrystallization from ethanol/ether had mp 190°-192° C. (dec.), $[\alpha]_{D23} = -88.7^\circ$ (2% MeOH).

EXAMPLE 12

A quantity of 1000 tablets each containing 100 mg of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) is produced from the following ingredients:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride hydrate (S,S,S)	100	g
Corn starch	50	g
Gelatin	7.5	g
Avicel (microcrystalline cellulose)	25	g
Magnesium stearate	2.5	g

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet press to form 1000 tablets each containing 100 mg of active ingredients.

EXAMPLE 13

A quantity of 1000 tablets each containing 200 mg of 2-[2-[[1-ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) is produced from the following ingredients:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S)	200	g
Lactose	100	g
Avicel	150	g
Corn starch	50	g
Magnesium stearate	5	g

The 2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) lactose and Avicel are admixed, then blended with the corn starch. Magnesium stearate is added. The dry mixture is compressed in a tablet press to form 1000, 505 mg tablets each containing 200 mg of active ingredient. The tablets are coated with a solution of Methocel E 15 (methyl cellulose) including as a color a lake containing yellow No. 6.

EXAMPLE 14

Two piece No. 1 gelatin capsules each containing 250 mg of 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S) are filled with a mixture of the following ingredients:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S)	250 g
Magnesium stearate	7 g
USP lactose	193 mg

EXAMPLE 15

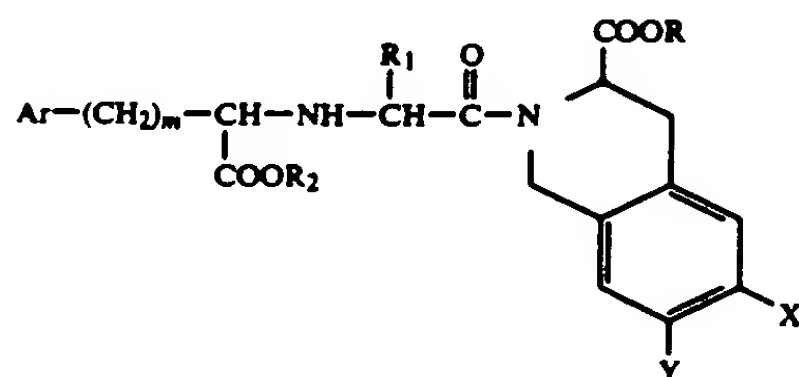
An injectable solution is produced as follows:

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S)	500 g
Methyl paraben	5 g
Propyl paraben	1 g
Sodium chloride	25 g
Water for injection q.s.	5 l

The active substance, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are then closed with presterilized rubber closures. Each vial contains 5 ml of solution in a concentration of 100 mg of active ingredient per ml of solution for injection.

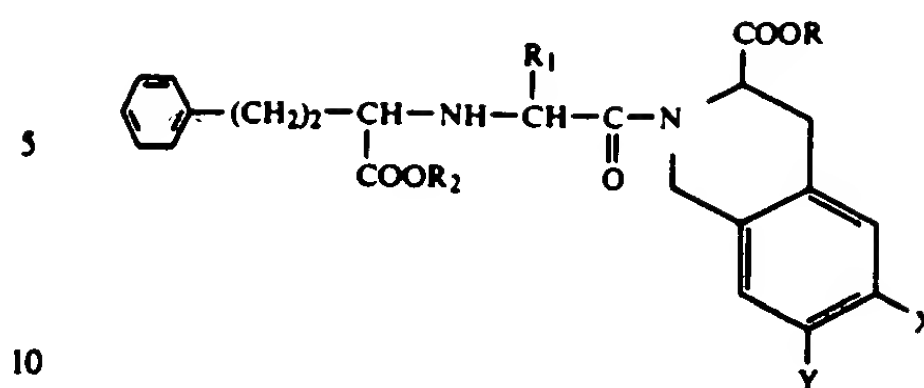
We claim:

1. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid having the formula



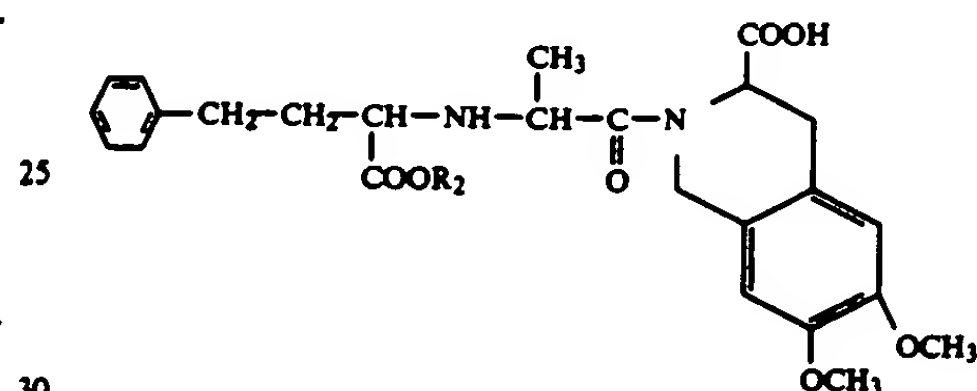
where R is hydrogen, lower alkyl or phenylalkyl; R₁ is hydrogen, lower alkyl, or benzyl; R₂ is hydrogen, or lower alkyl and Ar is phenyl, or substituted phenyl having 1 or 2 substituents selected from the group consisting of fluorine, chlorine, bromine, lower alkyl, lower alkoxy, hydroxy or amino; X and Y are independently hydrogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, or X and Y together are methylenedioxy; and m is 0 to 3; wherein lower alkyl, alkyl in the group phenylalkyl; and lower alkoxy has 1 to 4 straight or branched carbon atoms and the pharmaceutically acceptable salts thereof.

2. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 1 having the formula



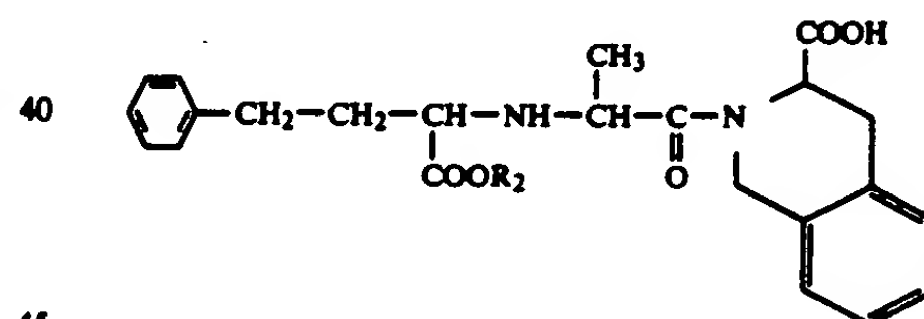
where R is hydrogen, t-butyl, or benzyl; R₁ is hydrogen or lower alkyl; R₂ is hydrogen, methyl or ethyl; X and Y are independently hydrogen, lower alkyl, hydroxy or lower alkoxy; and the pharmaceutically acceptable salts thereof.

3. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 2 having the formula



where R₂ is hydrogen, methyl or ethyl and the pharmaceutically acceptable salts thereof.

4. A substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 2 having the formula



where R₂ is hydrogen, methyl or ethyl and the pharmaceutically acceptable salts thereof.

5. The compound according to claim 2 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, phenylmethyl ester, maleate (S,S,S).

6. The compound according to claim 2 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, phenylmethyl ester, maleate (S,S,S).

7. The compound according to claim 2 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester, (S,S,S).

8. The compound according to claim 3 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S).

9. The compound according to claim 3 which is 2-[2-[[1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-

1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S).

10. The compound according to claim 4 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, hydrochloride, hydrate (S,S,S).

11. The compound according to claim 4 which is 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, hydrochloride, hemihydrate (S,S,S).

12. The compound according to claim 3 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline carboxylic acid, hydrochloride, (S,S,S).

13. The compound according to claim 4 which is 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, hydrochloride (S,S,S).

14. A pharmaceutical composition comprising 10 to 500 mg of a substituted acyl compound of a 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid or a mixture of compounds according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

15. A method of treating hypertension by administering an effective amount of a substituted acyl compound of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid according to claim 1 or a pharmaceutically acceptable salt thereof.

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bcc: Dr. R. A. Buchanan
Dr. R. M. Hodges
Dr. H. R. Kaplan*
Dr. J. R. Latts
Dr. J. G. Toole
Regulatory Affairs, MP*
✓IND File, AA*

* with attachment

IND

CI-906 Hydrochloride Capsules
Ref. No. 906/1

Submitted: MAY 17 1982

The Secretary of Health and Human Services
For the Commissioner of Food and Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Attached is our Notice of Claimed Investigational Exemption for CI-906 hydrochloride to clinically evaluate this angiotensin converting enzyme (ACE) inhibitor.

Please note in Item 10 of this Notice that the clinical pharmacology study to be conducted by our Dr. J. R. Latts and Dr. J. R. Goulet under Protocol 906-2 will utilize this compound as a solution. The purpose of using the drug in solution for this study is to obtain maximum absorption and consequently better pharmacokinetic data. Protocol 906-3, to be conducted by Dr. H. Gavras, and subsequent clinical studies will use the capsule formulations described under Items 2 and 3 of this Notice.

Very truly yours,

Original signed by
T. N. T. Olson

T. N. T. Olson, Ph.D.
Director
Regulatory Liaison and Compliance

TNTO-JEM:lmd

Attachment (Volumes 1-6)

In triplicate



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND FILE
COPY
MEDICAL AFFAIRS

MAY 27 1982

IND 20,336

Warner-Lambert Company
Pharmaceutical Research Division
2800 Plymouth Road
Ann Arbor, Michigan
48105

Dear Sir/Madam:

Dr. Olson

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: *20,336*

Sponsor:

Warner Lambert

Name of Drug:

CI-906 Hydrochloride Capsules

Date of Submission:

May 17, 1982

Date of Receipt:

May 19, 1982

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

cc: Regulatory Affairs, M.P.

RECEIVED

JUN 3 1982

IND

20, 336

Page 2

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

The 30-day restriction does not apply if the IND number was assigned for the emergency use of the drug in one patient only.

Should you have any questions concerning this IND, please call:

Ms. Jacqueline Knight

Consumer Safety Officer

(301) 443-

4730

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Bureau of Drugs, HFD-110
Attention: DOCUMENT CONTROL ROOM # 16B-30
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,


Natalia A. Morgenstern

Supervisory Consumer Safety Officer
Division of Cardio-Renal
Drug Products
Bureau of Drugs

CC:

Orig. File - pink

Division File - yellow

Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228b (1/82)

PARKE-DAVIS

Pharmaceutical Research Division

Warner-Lambert Company

NDA 19-885
Quinapril Hydrochloride
Tablets

January 26, 1989

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal
Drug Products (HFD-110)
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lipicky:

We are providing a new drug application for quinapril hydrochloride tablets for treatment of patients with hypertension. The tablets will be provided in strengths of 5 mg, 10 mg, 20 mg and 40 mg.

The patent information required by 21 U.S.C. 355(b)(1) is provided in section 13 of this NDA. In addition, this section documents that quinapril tablets for hypertension meet the requirements of 21 U.S.C. 355(j)(4)(D)(ii) and 355(c)(3)(D)(ii) for a five year market exclusivity period. A copy of section 13 immediately follows. A copy of this same information will also be forwarded shortly to FDA's Division of Information Resources.

A request for waiver of the requirement for in vivo bioavailability data on the 10 mg and 20 mg tablet strengths is made in the Human Pharmacokinetics and Bioavailability section. Documentation that these two strengths meet the requirements for granting a waiver are provided in Volume 39, page 06 000131.

On July 8, 1988 Parke-Davis representatives met with Dr. Wolters and Ms Danute Cunningham to address Chemistry, Manufacturing and Controls issues in this NDA. Minutes of this meeting were provided to IND 20,336 on August 10, 1988 (serial Number 471). At this meeting it was agreed that Parke-Davis would respond in the NDA to two letters from FDA dated July 1, 1988 and March 2, 1988. These responses are provided in the Chemistry, Manufacturing & Controls Section, beginning in Volume 3, page 03 000277.

Parke-Davis representatives also met twice with FDA on the clinical development of quinapril hydrochloride. On February 12, 1986, we met to review Phase 2 results and discuss the upcoming Phase 3 program. Parke-Davis' minutes of this meeting were provided to IND 20,336 on March 4, 1986 (serial number 167).

On May 9, 1988, a pre-NDA meeting was held with FDA. FDA suggestions made at this meeting and at a follow-up telephone conference have been incorporated in the NDA presentation. Minutes of the pre-NDA meeting and the follow-up telephone conference were provided to IND 20,336 on May 27, 1988 (serial number 463) and on July 19, 1988 (serial number 468), respectively.

While this NDA is for hypertension, quinapril has also been studied for treatment of patients with congestive heart failure (CHF). At the May 9, 1988 pre-NDA meeting FDA recommended not addressing CHF efficacy in the NDA. Therefore, CHF has not been addressed in the Integrated Summary of Efficacy. However, we have included CHF patients in the safety analyses, and reports of completed CHF studies have been included in the Clinical Data section.

Parke-Davis will test the stability of at least the first three lots of each strength of tablet in each package according to the stability testing protocol provided in Section 3, Volume 3, page 03 000095 of this application. In addition, the first three lots packaged at each packaging facility in this application will be tested according to this protocol.

Sincerely,

A handwritten signature in cursive script that reads "Jon Villaume". The signature is written in dark ink and is positioned above the printed name and title.

Jon Villaume
Director
Regulatory Affairs

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INFORMATION MANAGEMENT SYSTEM

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PAGE 1

CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE SER/SUPPL NO TITLE

17-MAY-82 1 INITIAL IND
CONTENT:

VOLUMES=6

ITEM 1: DRUG NAME, STRUCTURE AND METHOD OF
ADMINISTRATION.

ITEM 2: DRUG COMPONENTS OF THE FORMULATED DRUG.

ITEM 3: QUANTITATIVE COMPOSITION OF THE FORMULATED
DRUG.

ITEM 4: DRUG SOURCE AND PREPARATIONS OF THE NEW
DRUG SUBSTANCE.

ITEM 5: MANUFACTURING METHODS, FACILITIES, AND
CONTROLS FOR THE FORMULATED DRUG.

ITEM 6: PRECLINICAL AND OTHER PERTINENT
BACKGROUND INFORMATION

ITEM 7: INFORMATIONAL MATERIAL TO BE SUPPLIED
INVESTIGATORS AND DRUG LABEL.

ITEM 8: COMPANY REQUIREMENTS FOR CLINICAL
INVESTIGATORS

ITEM 9: NAME AND QUALIFICATIONS OF THE MONITORS
AND INVESTIGATORS.

ITEM 10: PROPOSED CLINICAL INVESTIGATIONS.

27-MAY-82 LETTER FROM FDA ACKNOWLEDGING RECEIPT (IND 20,336)
CONTENT:

LETTER FROM: FDA

RE: ACKNOWLEDGEMENT OF RECEIPT OF IND ON
19-MAY-82; NUMBER 20,336 ASSIGNED.

21-JUN-82 2 INFORMATION AMENDMENT
CONTENT:

REVISED PAGE
PG. 9

14-JUL-82 3 INFORMATION AMENDMENT
CONTENT:

REVISED PAGES FOR PR. 906-2
PGS. 1, 2, 3, 7

28-JUL-82 4 INFORMATION AMENDMENT
CONTENT:

REVISED PAGE RR X-740-00937
PG. 7

23-AUG-82 5 INFORMATION AMENDMENT
CONTENT:

REVISED PAGES FOR PR. 906-3
COMPLETE PROTOCOL
DATE: 12-JUN-82

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
20-DEC-82	12	PR. 906-5
CONTENT:		PR. 906-5 (J.R. LATTS & J.R. GOULET)
06-JAN-83	13	INFORMATION AMENDMENT
CONTENT:		RR 745-00541 AUTHOR: ANDERSON, J.A. ET AL DATE: 9-DEC-82 "TERATOLOGY STUDY IN RATS WITH CI-906"
06-JAN-83	14	INFORMATION AMENDMENT
CONTENT:		RR 745-00539 AUTHOR: ANDERSON, J.A. ET AL DATE: 20-DEC-82 "13-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS"
24-JAN-83	15	INFORMATION AMENDMENT
CONTENT:		REVISED PAGES FOR PR. 906-5 COMPLETE PROTOCOL DATE: 3-JAN-83
28-JAN-83	16	INFORMATION AMENDMENT
CONTENT:		RR 745-00552 AUTHOR: KIM, S.N. ET AL DATE: 29-DEC-82 "THIRTEEN-WEEK ORAL TOXICITY STUDY OF CI-906 IN MALE AND FEMALE ALBINO RATS"
23-FEB-83	17	INFORMATION AMENDMENT
CONTENT:		RR 724-00028 AUTHOR: PEARSE, S.B. DATE: 18-FEB-83 "A STUDY OF THE EFFECTS OF CI-906, AN INHIBITOR OF ANGIOTENSIN CONVERTING ENZYME, ON THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND RELATED CARDIOVASCULAR RESPONSES AFTER ANGIOTENSIN-1 CHALLENGE. PART 1: DOSE-RANGING STUDY IN TWO HEALTHY MEN. PART 2: DURATION OF ACTION STUDY IN FIVE HEALTHY MEN. (PR. 906-1, P.197)"

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
25-MAR-83 CONTENT:	18	INFORMATION AMENDMENT RR 250-01303 AUTHOR: BARSOUM, N.J. ET AL DATE: 15-MAR-83 "ACUTE ORAL TOXICITY STUDY OF CI-906 (PD 109452-2) IN MICE"
14-APR-83 CONTENT:	19	ANNUAL REPORT ISSUE DATE: 14-APR-83
07-JUN-83	20	PR. 906-6
07-JUN-83	21	PR. 906-8
01-JUL-83 CONTENT:	22	INFORMATION AMENDMENT RR 745-00608 AUTHOR: ANDERSON, J.A. ET AL DATE: 20-JUN-83 "EXPLORATORY RANGE-FINDING TERATOLOGY STUDY IN RABBITS WITH CI-906"
01-SEP-83 CONTENT:	23	INFORMATION AMENDMENT RR 250-01332 AUTHOR: BARSOUM, N.J. ET AL DATE: 26-AUG-83 "ACUTE ORAL TOXICITY STUDY OF CI-906 (PD109452-2) IN MICE"
27-SEP-83	24	PR. 906-10
19-OCT-83 CONTENT:	25	INFORMATION AMENDMENT RR 745-00639 AUTHOR: ANDERSON, J.A. ET AL DATE: 11-OCT-83 "TERATOLOGY STUDY IN RABBITS (CI-906)"
22-NOV-83 CONTENT:	26	INFORMATION AMENDMENT REVISED PAGE RR 745-00639 PG. 2 DATE" 18-NOV-83 CROSS REFERENCE: SERIAL #25

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
28-DEC-83 CONTENT:	27	INFORMATION AMENDMENT RR 250-01338 AUTHOR: BARSOUM, N.J. ET AL DATE: 2-DEC-83 "14 DAY REPEATED DOSE ORAL TOXICITY STUDY OF CI-906 IN MICE"
11-JAN-84	28	PR. 906-7
11-JAN-84	29	PR. 906-9
31-JAN-84 CONTENT:	30	INFORMATION AMENDMENT RR MEMO-939-0143 AUTHOR: SHAH, M. DATE: 23-JAN-84 "REVISED HPLC ASSAY OF CI-906 (ACE INHIBITOR) CAPSULES" CROSS REFERENCE: SERIAL #10
17-FEB-84 CONTENT:	31	SAFETY REPORT PATIENT NO.: 5 (TJP) PR. 906-6 AE: EXPERIENCED FACIAL SWELLING AND LARYNGEAL EDEMA WITH BREATHING DIFFICULTY. DRUG RELATED.
02-MAR-84 CONTENT:	32	INFORMATION AMENDMENT RR 740-01319 AUTHOR: WILEY, J.N. ET AL DATE: 9-FEB-84 "EVALUATION OF CI-906, CI-907, AND CI-925, POTENTIAL ACE INHIBITORS, AND REFERENCE DRUGS CAPTOPRIL AND ENALAPRIL IN THE MOUSE ANTIWRITHING TEST"
13-MAR-84 CONTENT:	33	SAFETY REPORT PATIENT NO.: 5 (TJP) PR. 906-6 AE: EXPERIENCED FACIAL SWELLING AND LARYNGEAL EDEMA WITH BREATHING DIFFICULTY. DRUG RELATED. FOLLOW-UP REPORT - SERIAL #31

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
16-MAR-84 CONTENT:	34	ANNUAL REPORT ISSUE DATE: 16-MARCH-84
16-MAR-84 CONTENT:	35	INFORMATION AMENDMENT RR 764-00188 AUTHOR: BORONDY, P.E. ET AL DATE: 28-FEB-84 "CI-906-14C: METABOLIC DISPOSITION STUDIES IN RATS AND MONKEYS, STABILITY TO DEESTERIFICATION AND ACE INHIBITION IN VITRO"
29-MAR-84 CONTENT:	36	SAFETY REPORT PATIENT NO.: 2 (RF) PR. 906-7 AE: DEATH DUE TO PATIENT'S ADVANCE CARDIAC DISEASE. NOT DRUG RELATED.
12-APR-84 CONTENT:	37	INFORMATION AMENDMENT REVISED PAGES RR 740-00942 COMPLETE REPORT DATE: 16-APR-82
12-APR-84 CONTENT:	38	INFORMATION AMENDMENT RR 724-00036 AUTHOR: LATTS, J.R. ET AL DATE: 23-MAY-84 "A CLINICAL PHARMACOLOGIC STUDY OF CI-906 HCL SOLUTION, PROTOCOL 906-2" RR MEMO-764-00156 AUTHOR: GRYCZKO C. ET AL DATE: 30-NOV-83 "ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL ADMINISTRATION OF CI-906 TO NORMAL HUMAN VOLUNTEERS. PROTOCOL 906-2"
12-APR-84 CONTENT:	38	INFORMATION AMENDMENT - CONTINUED RR MEMO-764-00131 AUTHORS: BORONDY, P.E. EASTON, M.L. DATE: 6-JUN-83 "INHIBITION OF PLASMA ANGIOTENSIN CONVERTING ENZYME (ACE) ACTIVITY FOLLOWING PERORAL ADMINISTRATION OF CI-906 TO NORMAL HUMAN VOLUNTEERS. PROTOCOL CI-906-2"

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
23-APR-84 CONTENT:		LETTER RE: FDA REQUEST FOR INFORMATION LETTER FROM: LIPICKY, R.J., M.D. RE: TERATOLOGY STUDIES IN RABBITS.
30-APR-84 CONTENT:	39	INFORMATION AMENDMENT RR 745-00686 AUTHOR: ANDERSON, J.A. ET AL DATE: 16-APR-84 "52-WEEK ORAL TOXICITY STUDY AND 104-WEEK CARCINOGEN BIOASSAY OF CI-906 IN RATS - 26-WEEK SUMMARY REPORT"
10-MAY-84 CONTENT:	40	SAFETY REPORT PATIENT NO.: 2 (RF) PR. 906-9 AE: DEATH DUE TO PATIENT'S ADVANCE CARDIAC DISEASE. NOT DRUG RELATED. WE WERE INADVERTENTLY ADVISED THAT THIS PATIENT WAS ENROLLED IN PR. 906-7. FOLLOW-UP REPORT - SERIAL #36
11-MAY-84 CONTENT:	41	IB UPDATE DATE: 24-APR-84 RR X-720-00952 AUTHOR: BAUKEMA, J. ET AL "INVESTIGATOR'S BRONCHURE - 906"
11-MAY-84 CONTENT:	42	INFORMATION AMENDMENT RR 740-01372 AUTHORS: GERMAIN, C.L. MERTZ, T.E. "COMPARISON OF THE EFFECTS OF CI-906, CAPTOPRIL AND ENALAPRIL (ACE INHIBITORS) ON THE BLOOD PRESSURE AND HEART RATE RESPONSES TO BRADYKININ BEFORE AND AFTER TREATMENT WITH INDOMETHACIN IN CONSCIOUS RABBITS"
11-MAY-84	43	PR. 906-20

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
14-MAY-84 CONTENT:	44	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO 23-APR-84 LETTER REQUESTING ADDITIONAL TERATOLOGY INFORMATION IN RABBITS. MEMO FROM DR. F.A. DE LA IGLESIA
18-MAY-84	45	PR. 906-14
18-MAY-84	46	PR. 906-17
18-MAY-84	47	PR. 906-18
18-MAY-84	48	PR. 906-19
18-MAY-84	49	PR. 906-22
18-MAY-84 CONTENT:	50	INFORMATION AMENDMENT RR: 745-00716 AUTHOR: JAYASEKARA, M.U. ET AL DATE: 14-MAY-84 "52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS - 26-WEEK SUMMARY REPORT"
31-MAY-84	51	PR. 906-15
07-JUN-84	52	PR. 906-26
07-JUN-84	53	PR. 906-13
07-JUN-84	54	PR. 906-21
07-JUN-84 CONTENT:	55	PROTOCOL AMENDMENT AMENDMENT NO. 1 PR. 906-9 DATE: 16-MAY-84 PROVIDES EXTENDED TREATMENT FOR PATIENTS RESPONDING TO CI-906 CAPSULE THERAPY.

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CI NUMBER= 906 APPL NUMBER= 20,336

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14-JUN-84	56	INFORMATION AMENDMENT
CONTENT: REVISED PAGES 745-00686 PGS. 15, 49, 50, 51, 52 DATE: 6-JUN-84 CROSS REFERENCE: SERIAL #39		
14-JUN-84	57	LETTER RE: PROTOCOL CANCELLATION
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. PR. 906-26 RE: CANCELLATION OF PROTOCOL.		
05-JUL-84	58	PR. 906-16
12-JUL-84	59	PR. 906-12
09-AUG-84	60	INFORMATION AMENDMENT
CONTENT: RR 724-00034 AUTHOR: LATTS, J.R. ET AL DATE: 3-AUG-84 "REPORT OF A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE PHARMACOKINETICS AND TOLERANCE OF CI-906 HCL IN NORMAL HEALTHY SUBJECTS (PROTOCOL 906-5)"		
09-AUG-84	61	LETTER RE: PROTOCOL CANCELLATION
CONTENT: LETTER: LIPICKY, RAYMOND J., M.D. PRS. 906-6, 10 RE: CANCELLATION OF PROTOCOL		
07-SEP-84	62	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-19 DATE: 31-AUG-84 PROVIDES FOR LONG-TERM, OPEN-LABEL TREATMENT WITH CI-906, 40.0 MG/DAY FOR PATIENTS.		
07-SEP-84	63	INFORMATION AMENDMENT
CONTENT: REVISED PAGE 745-00541 PG. 2 DATE: 28-AUG-84 CROSS REFERENCE: SERIAL #13		

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21-SEP-84 CONTENT:	64	INFORMATION AMENDMENT RR: 764-00268 AUTHORS: JORDAN, R.A. CHANG, T. DATE: 27-AUG-84 "THE EFFECT OF REPEATED ADMINISTRATION OF CI-906 ON THE RAT LIVER MICROSOMAL DRUG METABOLISM PARAMETERS"
21-SEP-84 CONTENT:	65	PROTOCOL AMENDMENT AMENDMENT NO. 1 PRS. 906-12, 16, 17, 20, 21 DATE: 31-AUG-84 PROVIDES FOR FURTHER TREATMENT WITH CI-906, 40.0 MG/DAY, ON AN OPEN-LABEL BASIS FOR PATIENTS.
09-OCT-84 CONTENT:	66	PROTOCOL AMENDMENT AMENDMENT NO. 1 PR. 906-22 DATE: 31-AUG-84 PROVIDES FOR FURTHER TREATMENT WITH CI-906, 40.0 MG/DAY, ON AN OPEN-LABEL BASIS FOR PATIENTS.
09-OCT-84 CONTENT:	67	INFORMATION AMENDMENT RR 745-00749 AUTHOR: ANDERSON, J.A. ET AL DATE: 17-SEP-84 "FERTILITY AND REPRODUCTION STUDIES IN RATS WITH CI-906"
24-OCT-84 CONTENT:	68	PROTOCOL AMENDMENT AMENDMENT NO. 1 PR. 906-15 DATE: 31-AUG-84 PROVIDES FOR FURTHER OPEN-LABEL TREATMENT WITH CI-906, 40.0 MG/DAY FOR PATIENTS.
06-NOV-84 CONTENT:	69	INFORMATION AMENDMENT RR 724-00039 AUTHOR: GOULET, J.R. ET AL DATE: 24-OCT-84 "REPORT OF A STUDY TO DETERMINE THE EFFECTIVE DOSE AND SAFETY OF CI-906 HCL IN PATIENTS WITH MILD TO MODERATE UNCOMPLICATED HYPERTENSION (PROTOCOL 906-4)"

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20-NOV-84	70	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 2		
PR. 906-19		
DATE: 1-NOV-84		
PROVIDES FOR LONG-TERM, OPEN-LABEL TREATMENT WITH		
CI-906, 80.0 MG/DAY FOR PATIENTS.		
17-DEC-84	71	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-7		
INCREASES THE TOTAL NUMBER OF PATIENTS TO BE		
TREATED FROM 12 TO 20 PATIENTS.		
AMENDMENT NO. 2		
PR. 906-9		
INCREASES THE TOTAL NUMBER OF PATIENTS TO BE		
TREATED FROM 12 TO 20 PATIENTS.		
26-DEC-84	72	INFORMATION AMENDMENT
CONTENT:		
RR 745-00776		
AUTHOR: ANDERSON, J.A. ET AL		
DATE: 18-DEC-84		
"52-WEEK ORAL TOXICITY STUDY AND 104-WEEK		
CARCINOGEN BIOASSAY OF CI-906 IN RATS - 52-WEEK		
SUMMARY REPORT"		
26-DEC-84	73	INFORMATION AMENDMENT
CONTENT:		
RR 745-00767		
AUTHOR: JAYASEKARA, M.U.		
DATE: 18-DEC-84		
"52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE		
DOGS"		
10-JAN-85	74	PR. 906-31
10-JAN-85	75	PR. 906-33
10-JAN-85	76	PR. 906-33
10-JAN-85	77	PR. 906-36

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10-JAN-85	78	PR. 906-44
10-JAN-85	79	PR. 906-27
10-JAN-85	80	PR. 906-28
10-JAN-85 CONTENT:	81	INFORMATION AMENDMENT RR 745-00779 AUTHOR: JAYASEKARA, M.U. ET AL DATE: 5-DEC-84 "THIRTEEN-WEEK MOUSE ORAL RANGE FINDING STUDY: CI-906"
17-JAN-85	82	PR. 906-11 (P.215)
17-JAN-85	83	PR. 906-48 (MUN/654)
17-JAN-85	84	PR. 906-49 (MUN/656)
17-JAN-85	85	PR. 906-52 (MUN/652)
17-JAN-85	86	PR. 906-53 (MUN/657)
17-JAN-85	87	PR. 906-54 (MUN/655)
17-JAN-85	88	PR. 906-35
17-JAN-85	89	PR. 906-43
17-JAN-85	90	PR. 906-46
31-JAN-85	91	PR. 906-41
31-JAN-85 CONTENT:	92	INFORMATION AMENDMENT AMENDMENT NO. 2 PR. 906-20 DATE: 1-NOV-84 PROVIDES FOR THE USE OF CI-906 80 MG/DAY ON AN OPEN-LABEL BASIS FOR PATIENTS WHO HAVE COMPLETED THE DOUBLE-BLIND PORTION OF THE STUDY.

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31-JAN-85 CONTENT:	93	INFORMATION AMENDMENT RR 724-00041 AUTHORS: LATTS, J.R. GOULET, J.R. DATE: 1-JAN-85 "REPORT OF A STUDY TO DETERMINE THE SAFETY AND MINIMUM ANTI-HYPERTENSIVE DOSE OF CI-906 HCL (PROTOCOL 906-3)"
07-FEB-85	94	PR. 906-55 (MUN/658)
07-FEB-85	95	PR. 906-56 (PAR/32)
07-FEB-85	96	PR. 906-37
14-FEB-85 CONTENT:	97	ANNUAL REPORT ISSUED DATE: 14-FEB-85
14-FEB-85 CONTENT:	98	PROTOCOL AMENDMENT AMENDMENT NO. 3 PR. 906-19 DATE: 15-NOV-84 PROVIDES FOR THE USE OF CI-906 CAPSULES, 60 MG/DAY ON AN OPEN-LABEL BASIS FOR PATIENTS WHO HAVE COMPLETED THE DOUBLE-BLIND POSTION
14-FEB-85 CONTENT:	99	INFORMATION AMENDMENT RR MEMO-764-00303 AUTHOR: GRYCZKO, C. ET AL DATE: 18-DEC-84 "ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL ADMINISTRATION OF CI-906 TO NORMAL HUMAN VOLUNTEERS AFTER ANGIOTENSIN-1 CHALLENGE. PROTOCOL 906-1"

REVISED PAGE RR 724-00028
PG. 1
DATE: 22-JAN-85
PR. 906-1

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14-FEB-85	100	PR. 906-40
14-FEB-85	101	PR. 906-45
21-FEB-85	102	PR. 906-30
21-FEB-85	103	PR. 906-32
21-FEB-85	104	PR. 906-38
21-FEB-85	105	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGES RR 745-00776 PGS. 49, 75, 76 AND 1282 DATE: 13-FEB-85 CROSS REFERENCE: SERIAL #10		
28-FEB-85	106	PR. 906-42
07-MAR-85	107	PR. 906-58 (MAD/104)
07-MAR-85	108	PR. 906-59 (MAD/105)
14-MAR-85	109	PR. 906-57 (PAR/34)
25-MAR-85	110	INFORMATION AMENDMENT
CONTENT:		
RR 724-00051 AUTHOR: GOULET, J.R. ET AL DATE: 21-MAR-85 "REPORT OF PROTOCOLS 906-6 AND -8: A 28-DAY DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY OF QUINAPRIL HYDROCHLORIDE (CI-906) IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION; AND PROTOCOL 906-10, A LONG-TERM EXTENSION OF PROTOCOL 906-6"		
06-MAY-85	111	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGES RR 764-00001 PGS. 1, 2/3, 6/7 AND 8/9 DATE: 10-APR-85 CROSS REFERENCE: SERIAL #1		

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20-MAY-85	112	NEW CO-INVESTIGATOR
CONTENT:		PR. 906-17 SHEFFIELD, L. THOMAS
28-JUN-85	113	IB UPDATE
CONTENT:		DATE: 6-JUN-85 RR X-720-02145 AUTHOR: BUAKEMA, J. "INVESTIGATOR'S BROCHURE: CI-906" SUPERCEDES RR X-720-00952.
16-JUL-85	114	NEW SUB-INVESTIGATOR
CONTENT:		PR. 906-13 PAYNE, TOM, M.D.
29-AUG-85	115	PR. 906-81
03-SEP-85	116	SAFETY REPORT
CONTENT:		PATIENT NO.: 6 (MJM) PR. 906-30 RE: DEVELOPED HYPOTENSION. PROBABLY DRUG RELATED.
16-SEP-85	117	SAFETY REPORT
CONTENT:		PATIENT NO.: 11 PR. 906-61 (P.254) AE: DEATH NOT DRUG RELATED
16-SEP-85	118	PR. 906-64
16-SEP-85	119	PR. 906-66
16-SEP-85	120	PR. 906-67
16-SEP-85	121	PR. 906-69

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DOC DATE	SER/SUPPL NO	TITLE
16-SEP-85	122	PR. 906-72
23-SEP-85 CONTENT:	123	LETTER RE: MANUFACTURING AND CONTROL LETTER TO: DIVISION OF CARDIO-RENAL RR MEMO-963-01027 RE: DATE ON OUR NEW 40 MG CONTROLLED RELEASE CAPSULES.
23-SEP-85 CONTENT:	124	SAFETY REPORT PATIENT NO.: 2 (GU) PR. 906-11 (P.215) AE: LIGHT-HEADEDNESS AND WOOZINESS IMMEDIATELY AFTER THE ADDITION OF CHLORTHALIDONE 25 MG TO QUINAPRIL 40 MG DAILY. SYMPTOMS RESOLVED ON DIURETIC WITHDRAWAL. DRUG RELATED. PATIENT NO.: 22 (MH) PR. 906-11 (P.215) AE: BUSSING IN HEAD, HEAVINESS AND ACHING IN ARMS AND LEGS FROM THE DAY AFTER THE ADDITION OF CHLORTHALIDONE 25 MG TO QUINAPRIL 40 MG DAILY. SYMPTOMS RESOLVED ON DIURETIC WITHDRAWAL. DRUG RELATED.
23-SEP-85 CONTENT:	124	SAFETY REPORT - CONTINUED PATIENT NO.: 1 (DB) PR. 906-11 (P.215) AE: COMPLETE RIGHT HEMIPARESIS 5 DAYS AFTER THE ADDITION OF CHLORTHALIDONE 25 MG TO QUINAPRIL 40 MG DAILY. DRUG RELATED. PATIENT NO.: 10 (KW) PR. 906-11 (P.215) AE: NAUSEA, WEAKNESS, FATIGUE AND GENERALISED ACHES AND MUSCLE CRAMPS STARTING 3 DAYS AFTER MUSCLE CRAMPS STARTING 3 DAYS AFTER CHLORTHALIDONE 25 MG DAILY ADDED TO QUINAPRIL 40 MG DAILY. DRUG RELATED. PATIENT NO.: 24 (EB) PR. 906-11 (P.215) AE: MELAENA AND HB DROP FROM 14.9 TO 10.6 G/DL. DRUG RELATED

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DOC DATE	SER/SUPPL NO	TITLE
23-SEP-85	124	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 31 (PC)		
PR. 906-11 (P.215)		
AE: DIZZINESS, PALPITATIONS, BREATHLESSNESS AND FEELING GENERALLY UNWELL ON THE FIFTH DAY AFTER DIURETIC ADDED.		
DRUG RELATED		
01-OCT-85	125	INFORMATION AMENDMENT
CONTENT:		
RR 745-00844		
AUTHOR: ANDERSON, J.A.		
DATE: 13-SEP-85		
"PERINATAL AND POSTNATAL STUDY IN RATS WITH CI-906"		
01-OCT-85	126	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PRS. 906-31, 32, 33, 34, 36, 37, 38, 40, 41, 43, 44, 45, 46		
DATE: 17-JUN-85		
PROVIDE ADDITIONAL BLOOD PRESSURE MEASUREMENTS.		
01-OCT-85	127	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 2		
PRS. 906-15, 16, 17, 18, 21 AND 22		
DATE: 10-JUN-85		
PROVIDES AND ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN-LABEL PERIOD OF TREATMENT FOR PATIENTS RESPONDING TO QUINAPRIL HYDROCHLORIDE.		
01-OCT-85	128	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENTS NO. 4		
PR. 906-19		
DATE: 10-JUN-85		
PROVIDES AN ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN-LABEL PERIOD OF TREATMENT FOR PATIENTS RESPONDING TO QUINAPRIL HYDROCHLORIDE.		
AMENDMENT NO. 5		
PR. 906-19		
DATE: NONE		
ALLOWS FOR 24 HOUR BLOOD PRESSURE MONITORING TO BE OBTAINED IN ALL PATIENTS IN THE OPEN-LABEL PERIOD WHO ARE RECEIVING CI-906 AS MONOTHERAPY FOR THEIR MILD TO MODERATE HYPERTENSION.		

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01-OCT-85	129	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 3		
PR. 906-15		
DATE: NONE		
ALLOWS 24 HOUR BLOOD PRESSURE MONITORING TO BE OBTAINED IN ALL PATIENTS IN THE OPEN-LABEL PERIOD WHO ARE RECEIVING CI-906 AS MONOTHERAPY FOR THEIR MILD TO MODERATE HYPERTENSION.		
AMENDMENT NO. 2		
PRS. 906-33, 44		
DATE: NONE		
ALLOW 24 HOUR BLOOD PRESSURE MONITORING TO BE OBTAINED IN ALL PATIENTS IN THE OPEN-LABEL PERIOD WHO ARE RECEIVING CI-906 AS MONOTHERAPY FOR THEIR MILD TO MODERATE HYPERTENSION.		
14-OCT-85	130	SAFETY REPORT
CONTENT:		
PATIENT NO.: 21 (SSH)		
PR. 906-11 (P.215)		
AE: HYPERSENSITIVITY REACTION		
DRUG RELATED.		
15-OCT-85	131	PR. 906-65
15-OCT-85	132	PR. 906-73
15-OCT-85	133	PR. 906-74
21-OCT-85	134	SAFETY REPORT
CONTENT:		
PATIENT NO.3		
PR. 906-62 (UNITED KINGDOM)		
NOT DRUG RELATED.		
PATIENT NO. 6		
PR. 906-62 (UNITED KINGDOM)		
NOT DRUG RELATED.		
PATIENT NO. 11		
PR. 906-62 (UNITED KINGDOM)		
NOT DRUG RELATED.		

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DOC DATE	SER/SUPPL NO	TITLE
29-OCT-85	135	PR. 906-80 (MUN/664)
29-OCT-85	136	INFORMATION AMENDMENT
CONTENT: RR 740-01803 AUTHOR: FINK, G. ET AL DATE: 22-OCT-85/22/85 BY D. M. COHEN. "EFFECTS OF SEVERAL ACE INHIBITORS ON BRAIN CONVERTING ENZYME ACTIVITY IN NORMOTENSIVE RATS"		
29-OCT-85	137	INFORMATION AMENDMENT
CONTENT: REVISED PAGE RR X-720-02145 PG. 11 DATE: 25-SEP-85 CROSS REFERENCE: SERIAL #113		
29-OCT-85	138	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 2 PR. 906-12 DATE: 10-JUN-85 PROVIDES AN ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN-LABEL PERIOD OF TREATMENT FOR PATIENTS RESPONDING TO QUINAPRIL HYDROCHLORIDE (CI-906).		
11-NOV-85	139	SAFETY REPORT
CONTENT: PATIENT NO.: 10 (LTT) PR. 906-34 AE: CARDIAC ARRHYTHMIA.		
21-NOV-85	140	PR. 906-99
27-NOV-85		LETTER RE: FDA REQUEST FOR INFORMATION
CONTENT: LETTER FROM: LIPICKY, RAYMOND J., M.D. RE: FDA REVIEWED INITIAL SUBMISSION WITH SEVERAL RECOMMENDATIONS AND REQUEST FOR INFORMATION.		
24-DEC-85	141	LETTER RE: REQUEST FOR INFORMATION
CONTENT: LETTER TO: LIPICKY, RAYMON J., M.D. RE: PROOF-OF-EFFICACY CLINICAL STUDIES: 1) TWO PROTOCOLS. 2) PRELIMINARY REPORT OF PHASE 2 MULTICENTER STUDIES. 3) REQUEST PERMISSION TO ADMINISTER THIS DRUG TO WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT PREGNANT OR NURSING AND ARE USING A RELIABLE METHOD OF CONTRACEPTION CONTROL		

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30-DEC-85	142	SAFETY REPORT
CONTENT:		PATIENT NO.: 24 (FLS) PR. 906-15 AE: GASTROINTESTINAL BLEED
08-JAN-86	143	SAFETY REPORT
CONTENT:		PATIENT NO.: 17 (RL) PR. 906-36 AE: DEVELOPED ATRIAL FIBRILLATION AND WAS HYPOKALEMIC. NOT DRUG RELATED.
10-JAN-86	144	PR. 906-83
10-JAN-86	145	PR. 906-84
10-JAN-86	146	PR. 906-85
10-JAN-86	147	PR. 906-86
10-JAN-86	148	PR. 906-88
10-JAN-86	149	PR. 906-89
10-JAN-86	150	PR. 906-90
10-JAN-86	151	PR. 906-91
10-JAN-86	152	PR. 906-92
15-JAN-86	153	SAFETY REPORT
CONTENT:		PATIENT NO.: 11 (NONE) PR. 906-17 AE: CAROTID ENDARTERECTOMY FOLLOWING A SYCOPAL EPISODE. AE 001-0906-860002-00

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17-JAN-86 CONTENT:	154	SAFETY REPORT PATIENT NO.: 19 (OR) PR.: INTERNATIONAL STUDY AE: ACUTE MYOCARDIAL INFARCTION WHILE RECEIVING PLACEBO.
24-JAN-86 CONTENT:	155	LETTER RE: CONFIRMATION OF MEETING LETTER TO: LIPICKY, RAYMOND J., M.D. RE: CONFIRMATION OF 12-FEB-86, 10 AM TO NOON MEETING IN ROCKVILLE, MARYLAND.
30-JAN-86 CONTENT:	156	ANNUAL REPORT ISSUED DATE: 20-JAN-86
31-JAN-86	157	PR. 906-82
31-JAN-86	158	PR. 906-63
31-JAN-86	159	PR. 906-68
31-JAN-86	160	PR. 906-75
31-JAN-86	161	PR. 906-76
10-FEB-86	162	PRS. 906-100, 102, 103, 104, 105, 106, 107, 108 (WLI 9-009-0)
17-FEB-86 CONTENT:	163	SAFETY REPORT PATIENT NO.: 3 (KAL) PR. 906-72 AE: CARDIA ARREST AND WAS RESUSCITATED. NOT DRUG RELATED. AE 001-0906-860003-00
18-FEB-86 CONTENT:	164	SAFETY REPORT PATIENT NO.: 19 (NONE) PR. 906-30 AE: SUDDEN HEARING LOSS IN THE LEFT EAR. NOT DRUG RELATED. AE 001-0906-860004-00

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DOC DATE	SER/SUPPL NO	TITLE
18-FEB-86	165	PR. 906-87
03-MAR-86	166	SAFETY REPORT
CONTENT:		
PATIENT NO.: 13 (NONE)		
PR. 906-45		
AE: A TRANSIENT ARM NUMBNESS AND SPEECH DIFFICULTY.		
DRUG RELATED.		
AE 001-0906-860005-00		
04-MAR-86	167	MINUTES OF FDA MEETING
CONTENT:		
DATE: 12-FEB-86		
FDA MEETING CONCERNING THE QUINAPRIL HYDROCHLORIDE CLINICAL PROGRAM.		
06-MAR-86	168	SAFETY REPORT
CONTENT:		
PATIENT NO.: 3 (NONE)		
PR. 890-137		
AE: ICTERUS, CHOLOSTRASIS, DIAGNOSTIC MEASURES REVEALED PANCREATIC NEOPLASM AS CAUSE OFT CHOLOSTRASIS.		
NOT DRUG RELATED.		
AE 049-0906-860001-00		
06-MAR-86	168	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 6 (AF)		
PR. 044-0906-860004-01		
AE: TRANSIENT ISCHEMIC ATTACH (CEREBRAL)		
DRUG RELATED.		
AE 044-0906-860004-00		
06-MAR-86	168	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 19 (WMY)		
PR. 9-003-4		
AE: TRANSIENT CEREBROVASCULAR ACCIDENT.		
AE 044-0906-860005-00		
06-MAR-86	169	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		
LETTER TO: LIPICKY, RAYMOND J., M.D.		
RE: FDA'S 27-NOV-85 REQUEST FOR INFORMATION.		
1) RESPONSE BY MR. J.A. BOONSTRA CONCERNING THE ADDITIONAL MANUFACTURING AND CONTROLS DATA.		
2) RESPONSE BY MR. O.R. CANIS CONCERNING THE CONTAINER AND CLOSURE SYSTEM USED TO PACKAGE THE DRUG.		
3) REVISED PAGE X-720-02145		

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DOC DATE	SER/SUPPL NO	TITLE
14-MAR-86	170	SAFETY REPORT
CONTENT:		
PATIENT NO.: 19 (WDD)		
PR. 906-30		
AE: DEVELOPED A SUDDEN HEARING LOSS IN THE LEFT EAR.		
NOT DRUG RELATED.		
FOLLOW-UP REPORT - SERIAL #164		
24-MAR-86	171	SAFETY REPORT
CONTENT:		
PATIENT NO.: 13 (KEF)		
PR. 906-45		
AE: TRANSIENT ARM NUMBNESS AND SPEECH DIFFICULTY. DIAGNOSED AS NERVE PALSY.		
NOT DRUG RELATED.		
FOLLOW-UP REPORT - SERIAL #166		
AE 001-0906-860005-01		
24-MAR-86	172	SAFETY REPORT
CONTENT:		
PATIENT NO.: NONE (JH)		
PR. 906-48		
AE: CEREBRAL INSULT DURING THE OPEN LABEL PERIOD OF THE STUDY.		
AE 043-0906-860002-00		
24-MAR-86	172	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 21 (JGM)		
SPAIN		
AE: URINARY RETENTION OF APPROXIMATELY 25 DAYS.		
AE 034-0906-860002-00		
25-MAR-86	173	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (LTT)		
PR. 906-34		
AE: HAD A CARDIAC ARRHYTHMIA. SECONDARY TO HYPOKALEMIA.		
FOLLOW-UP - SERIAL #139		
27-MAR-86	174	PR. 906-60/INFORMATION AMENDMENT
CONTENT:		
RR MEMO-764-00505		
AUTHORS: FERRY, J.		
COLBURN, W.		
DATE: 17-FEB-86		
"CI-906: PROPOSED STUDY IN HUMAN SUBJECTS WITH 14C-LABELED DRUG: ESTIMATION OF RADIATION IMPACT ON TARGET ORGANS"		

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27-MAR-86	175	INFORMATION AMENDMENT
CONTENT: RR 764-00441 AUTHOR: TAYLOR, M. ET AL DATE: 13-FEB-86 "CI-906 AND CI-928: A VALIDATED GAS CHROMATOGRAPHIC ASSAY FOR HUMAN PLASMA SAMPLES"		
27-MAR-86	176	PRS. 906-114 TO 906-127, 131, 133, 134, 136
08-APR-86	177	SAFETY REPORT
CONTENT: PATIENT NO.: 3 (KAL) PR. 907-72 AE: HAD A CARDIAC ARREST AND WAS RESUSCITATED. NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #163 AE 001-0906-860003-01		
10-APR-86	178	PR. 906-93
10-APR-86	179	PRS. 906-128, 129, 130, 132
14-APR-86	180	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. DATE: 11-APR-86 RE: ADDITIONAL MANUFACTURING AND CONTROLS DATA AS REQUESTED IN FDA 27-NOV-85 LETTER.		
14-APR-86	181	PR. 906-223
21-APR-86	182	PR. 906-95
21-APR-86	183	PR. 906-77
21-APR-86	184	PRS. 906-94 & 906-966
21-APR-86	185	SAFETY REPORT
CONTENT: PATIENT NO.: 16 (TCO) PR. 906-33 AE: EXPERIENCED SHORTNESS OF BREATH WITH BRONCHIAL SPASM. DRUG RELATED. AE 001-0906-860006-00		

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21-APR-86 185 SAFETY REPORT - CONTINUED
CONTENT:

PATIENT NO.: 1 (WEP)
PR. 906-86
AE: EXPERIENCED CHEST PAIN AND SHORTNESS OF BREATH
AND SYNCOPE.
AE 001-0906-860007-00

23-APR-86 186 SAFETY REPORT
CONTENT:

PATIENT NO.: 11 (JHO)
PR. 906-91
AE: DEVELOPED ARTHRALGIA, BACKACHE AND A LOW
GRADE FEVER. MAY BE THE RESULT OF A VIRAL
SYNDROME.
AE 001-0906-860008-00

28-APR-86 187 PR. 906-91

28-APR-86 188 PR. 906-202

29-APR-86 189 LETTER RE: SUBMISSION CORRECTION
CONTENT:

LETTER TO: CARDIO-RENAL DIVISION
RE: INADVERTENTLY IDENTIFIED 28-APR-86, SERIAL
NO. 188, IND AS 20,898.

01-MAY-86 190 SAFETY REPORT
CONTENT:

PATIENT NO.: 1 (MA)
PR. 85-791
AE: DEVELOPED SYNCOPE.
MAY BE DRUG RELATED.
AE 049-9048-860001-00

01-MAY-86 190 SAFETY REPORT - CONTINUED
CONTENT:

PATIENT NO.: 2 (NONE)
PR. 9-009-0 - STUDY NO. 85-791
AE: DEVELOPED FACIAL SRYTHEMA, CYANOSIS,
ARTHRALGIA AND NAUSEA.
DRUG RELATED.
AE 032-906-860001-00

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DOC DATE	SER/SUPPL NO	TITLE
02-MAY-86	191	SAFETY REPORT
CONTENT: PATIENT NO.: 1 (WEP) PR. 906-86 AE: CHEST PAIN, SHORTNESS OF BREATH AND SYNCOPE. AE 001-0906-860007-01		
05-MAY-86	192	PR. 906-209 (MUN/683)
05-MAY-86	193	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 74 75, 76, 77 DATE: 7-MAR-86 WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT PREGNANT OR BREAST FEEDING AND WHO USE A RELIABLE METHOD OF CONTRACEPTION FOR THE DURATION OF THE STUDY MAY PARTICIPATE.		
07-MAY-86	194	SAFETY REPORT
CONTENT: PATIENT NO.: 24 (FLS) PR. 906-15 AE: HOSPITALIZED WITH A GASTROINTESTINAL BLEEDING. DRUG RELATED. FOLLOW-UP REPORT - SERIAL #142		
13-MAY-86	195	PRS. 906-137 & 138
13-MAY-86	196	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PRS. 906-114, 115, 116, 117, 118, 119, 120, 121, 123, 124, 125, 126, 127, 128, 129, 130, 131, 131, 133, 134 AND 136 DATE: 1-MAR-86 PROVIDES FOR HOURLY BLOOD PRESSURE AND HEART RATE MEASUREMENT AND RECORDING FOR PATIENTS. CROSS REFERENCE: SERIAL #176		
13-MAY-86	197	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 42 DATE: 17-JUN-85 PROVIDE FOR ADDITIONAL BLOOD PRESSURE MEASUREMENTS IN THE STUDY. CROSS REFERENCE: SERIAL #106 AMENDMENT NO. 1 PRS. 906-20, 43 DATE: 20-AUG-85		

PROVIDE FOR TWICE A DAY DOSING OF QUINAPRIL
HYDROCHLORIDE (CI-906) IN THE OPEN-LABEL PHASE
OF PROTOCOL 906 CHLORTHALIDONE IN MILD TO
MODERATE HYPERTENSIVE PATIENTS.
CROSS REFERENCE: SERIAL #43

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15-MAY-86 LETTER RE: CONFIRMATION OF AGREEMENT
CONTENT:

CROSSFILE IND 22,996, SERIAL NO. 179
LETTER TO: LIPICKY, RAYMOND J., M.D.
RE: CONFIRMING THAT FDA HAS NO OBJECTIONS TO USING
EITHER THE TREADMILL OR BICYCLE EROGMETER TEST
IN EITHER/OR BOTH STUDIES (CI-914 AND/OR
CI-906).

20-MAY-86 198 PROTOCOL AMENDMENTS
CONTENT:

AMENDMENT NO. 1
PRS. 82, 83, 84, 85, 86, 87, 88, 93, 94, 95 AND
96
DATE: 14-FEB-86
CHANGES THE DOSEAGE OF HYDROCHLOROTHIAZIDE TO
25 MG ONCE A DAY IN THE PLACEBO-BASELINE AND
DOUBLE-BLIND PERIOD.

AMENDMENT NO. 2
PRS. 82, 83, 84, 85, 86, 88, 93, 94, 95 AND 96
DATE: 14-FEB-86
PROVIDE FOR THE PARTICIPATION OF WOMEN OF CHILD-
BEARING POTENTIAL WHO ARE NOT PREGNANT OR BREAST
FEEDING, AND WHO ARE ON A RELIABLE CONTRACEPTION
FOR THE THE DURATION OF THEIR PARTICIPATION.

20-MAY-86 198 PROTOCOL AMENDMENTS - CONTINUED
CONTENT:

AMENDMENT NO. 3
PRS. 82, 83, 84, 85, 86, 94 AND 96
DATE: 28-APR-86
PROVIDES FOR THE EXCLUSION OF PATIENTS WITH
ANTI-NUCLEAR ANTIGEN (ANA) TITERS OF GREATER THAN
1:40 AT THE TIME OF SCREENING, FROM ENTRY INTO
THE PLACEBO BASELINE OR DOUBLE-BLIND PERIOD.

20-MAY-86 199 PROTOCOL AMENDMENT
CONTENT:

AMENDMENT NO.: 1
PRS. 906-11, CENTERS P.215, P.216, P.217, P.219,
P.220 AND P.221
EXTENDS THE OPEN-LABELED PORTION OF THIS STUDY FOR
A SECOND YEAR.

27-MAY-86 200 PR. 906-78

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DOC DATE	SER/SUPPL NO	TITLE
27-MAY-86	201	SAFETY REPORT
CONTENT:		
PATIENT NO.: 16 (HJ)		
PR. 906-48		
AE: DEATH		
NOT DRUG RELATED.		
AE 043-0906-860003-00		
29-MAY-86	202	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (LWS)		
PR. 906-21		
AE: DEVELOPED HAIR LOSS.		
AE 001-0906-860009-00		
29-MAY-86	203	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (MA)		
PR. 85-791		
AE: DEVELOPED PALPITATIONS, FLUSH, ARTHRALGIA AND NAUSEA.		
DRUG RELATED.		
AE 032-9016-860001-01		
05-JUN-86	204	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (SMF)		
PR. 906-89		
AE: EXPERIENCED A SYNCOPE EPISODE.		
NOT DRUG RELATED.		
AE 001-0906-860010-00		
05-JUN-86	205	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 1		
PR. 906-78		
DATE: 7-MAR-86		
PROVIDES FOR THE PARTICIPATION OF WOMEN OF		
CHILDBEARING POTENTIAL WHO ARE NOT PREGNANT OR		
BREAST FEEDING, AND WHO ARE ON A RELIABLE		
CONTRACEPTIVE FOR THE DURATION OF THEIR		
PARTICIPATION IN THIS STUDY.		
10-JUN-86	206	SAFETY REPORT
CONTENT:		
PATIENT NO.: 7 (NONE)		
PR. 906-89		
AE: EXPERIENCED VIOLENT NAUSEA AND VOMITING 1-2		
HOURS AFTER TAKING EACH DOSE OF MEDICATION.		
DRUG RELATED.		
AE 001-0906-860011-00		

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DOC DATE	SER/SUPPL NO	TITLE
10-JUN-86	207	INFORMATION AMENDMENT
CONTENT: RR 764-00523 AUTHOR: FERRY, J. ET AL DATE: 16-MAY-86 "CLINICAL BIOPHARMACEUTICAL STUDY OF TWO NEW PROTOTYPE FORMULATION CAPSULES OF QUINAPRIL (CI-906) AND AN IMMEDIATE-RELEASE CAPSULE. PROTOCOL 906-81"		
12-JUN-86	208	PR. 906-211
17-JUN-86	209	SAFETY REPORT
CONTENT: PATIENT NO.: 10 (HJ) PR. 906-48 AE: DEATH DUE TO A CEREBRAL INSULT. NOT DRUG RELATED. AE 043-0906-860002-01		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT: PATIENT NO.: 1 (K) PR. 890-211 AE: INCREASE IN URIC ACID AND CREATININE LEVEL.		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT: PATIENT NO.: 8 (NONE) PR. 891-157 AE: SEVERE NAUSEA .		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT: PATIENT NO.: NONE (TAR) PR. 9-003-4 AE: DEATH - CEREBROVASCULAR ACCIDENT. NOT DRUG RELATED.		
17-JUN-86	209	SAFETY REPORT - CONTINUED
CONTENT: PATIENT NO.: 16 (HN) PR. 906-48 AE: MYOCARDIAL INFARCTION. NOT DRUG RELATED.		

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DOC DATE	SER/SUPPL NO	TITLE
17-JUN-86	210	INFORMATION AMENDMENT
CONTENT: RR MEMO-764-00554 AUTHORS: FERRY, J. COLBURN, W. DATE: 30-APR-86 "PHARMACOKINETIC ASSESSMENT OF CI-928 FOLLOWING MULTIPLE DOSE ADMINISTRATION OF CI-906 TO PATIENT WITH MILD TO MODERATE HYPERTENSION. PROTOCOLS 906: 12-22"		
17-JUN-86	211	PR. 906-79
17-JUN-86	212	PR. 906-213 (WLI-9-015-0)
23-JUN-86	213	SAFETY REPORT
CONTENT: PATIENT NO.: 3 (KAL) PR. 906-72 AE: HAD A CARDIAC ARREST AND WAS RESUSCITATED. NOT DRUG RELATED. AE 001-0906-860003-02		
23-JUN-86	214	PROTOCOL AMENDMENTS
CONTENT: AMENDMENT NO. 1 PR. 906-79 DATE: 7-MAR-86 PERMITS THE INCLUSION OF WOMEN OF CHILDBEARING POTENTIAL. AMENDMENT NO. 2 PR. 906-79 DATE: 10-APR-86 ALLOWS PATIENTS TO ENROLL WITH FEV1 OF FVC OF AT LEAST 50% OF NORMAL.		
23-JUN-86	215	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 2 PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 74, 75, 76, 77 AND 78 DATE: 10-APR-86 ALLOWS ENROLLMENT OF PATIENTS WITH FEV1 OR FVC OF AT LEAST 50% OF NORMAL.		

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DOC DATE	SER/SUPPL NO	TITLE
02-JUL-86	216	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (LWS)		
PR. 906-21		
AE: DEVELOPED HAIR LOSS.		
NOT DRUG RELATED.		
AE 001-0906-860009-01		
02-JUL-86	217	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (CL)		
PR. 9-003-3		
AE: FLUID RETENTION AND OTHER SYMPTOMS.		
MAY BE DRUG RELATED.		
AE 033-0906-860003-02		
02-JUL-86	218	SAFETY REPORT
CONTENT:		
PATIENT NO.: 45 (CA)		
PR. 215-906-11		
AE: EXPERIENCED MUSCLE WEAKNESS, CRAMPS, POTASSIUM		
LOSS, ALKALOSIS AND IRON DEFICIENCY ANEMIA.		
NOT DRUG RELATED.		
AE 044-0906-860001-01		
02-JUL-86	219	PR. 906-144 (WLI 9-030-0)
02-JUL-86	220	PR. 906-188 (WLI 9-016-0)
10-JUL-86	221	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 1		
PRS. 906-89, 90, 91, 92, 122, 137 AND 138		
DATE: 14-FEB-86		
CHANGES DOSAGE OF HYDROCHLOROTHIAZIDE TO 25 MG		
ONCE A DAY IN THE PLACEBO BASELINE AND THE		
DOUBLE-BLIND PERIOD.		
AMENDMENT NO. 2		
PRS. 87, 89, 90, 91, 92 AND 124		
DATE: 28-APR-86		
PROVIDES FOR THE EXCLUSION OF PATIENTS WITH		
ANTI-NUCLEAR ANTIGEN (ANA) TITERS OF GREATER		
THAN 1:40 AT THE TIME OF SCREENING.		
AMENDMENT NO. 3		
PRS. 88, 89, 90, 91, 92 AND 93		
DATE: 28-APR-86		
PROVIDES FOR THE EXCLUSION OF PATIENTS WITH ANTI-		
NUCLEAR ANTIGEN (ANA) TITERS OF GREATER THAN		
1:40 AT THE TIME OF SCREENING.		

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DOC DATE	SER/SUPPL NO	TITLE
10-JUL-86	222	PR. 906-109 (WLI-9-009-0)
10-JUL-86	223	PR. 906-110 (WLI-9-009-0)
14-JUL-86	224	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (KIN)		
PR. 906-66		
AE: DEATH FROM A PROBABLE ARRHYTHMIA.		
AE 001-0906-860012-00		
14-JUL-86	225	PROTOCOL AMENDMENTS
CONTENT:		
AMENDMENT NO. 1		
PR. 35		
DATE: 17-JUN-85		
PROVIDE FOR ADDITIONAL BLOOD PRESSURE MEASUREMENTS		
AMENDMENT NO. 2		
PRS. 906-31, 35, 36, 37, 38, 42, 45 AND 46		
DATE: 15-JUL-86		
PROVIDES FOR AN ADDITIONAL 12 MONTHS CONTINUATION		
OF THE LONG-TERM, OPEN LABEL PERIOD OF TREATMENT		
FOR PATIENTS RESPONDING TO QUINAPRIL		
HYDROCHLORIDE.		
AMENDMENT NO. 3		
PRS. 906-33, 35, 43, 44 AND 45		
DATE: 15-JUL-86		
PROVIDES FOR AN ADDITIONAL 12 MONTHS CONTINUATION		
OF THE LONG-TERM, OPEN LABEL PERIOD OF TREATMENT		
FOR PATIENTS RESPONDING TO QUINAPRIL		
HYDROCHLORIDE.		
14-JUL-86	225	PROTOCOL AMENDMENT - CONTINUED
CONTENT:		
AMENDMENT NO. 4		
PRS. 15 AND 44		
DATE: 1-NOV-84		
ALLOWS FOR THE USE OF CI-906 80.0 MG/DAY IN THE		
LONG-TERM PORTION OF THE DOSE RESPONSE STUDY FOR		
THOSE PATIENTS WHO HAVE NOT SHOWN THE DESIRED		
EFFICACY IN LOWERING BLOOD PRESSURE AT LOWER		
DOSES OF CI-906, AND WHO ARE ALSO FREE FROM ANY		
CLINICALLY SIGNIFICANT SIDE EFFECTS.		
21-JUL-86	226	PRS. 906-151, 152, 153, 154, 155, 163

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DOC DATE	SER/SUPPL NO	TITLE
21-JUL-86	227	INFORMATION AMENDMENT
CONTENT:		
RR 740-01706		
AUTHOR: UHLENDORF, P.D. ET AL		
DATE: 30-JUN-86		
"LIPID-REGULATING EFFECT OF CI-906, CI-907, AND CI-925 IN CHOLESTEROL-FED RATS: COMPARISON TO REFERENCE ACE INHIBITORS"		
RR 764-00556		
AUTHOR: FERRY, J. ET AL		
DATE: 11-JUN-86		
"EFFECT OF FOOD ON CI-906 (QUINAPRIL) AND CI-928 PHARMACOKINETICS FOLLOWING ORAL DOSING OF CI-906 TO HEALTHY SUBJECTS. PROTOCOL 906-80"		
28-JUL-86	228	SAFETY REPORT
CONTENT:		
PATIENT NO.: 5 (PHH)		
PR. 906-73		
AE: WORSENING OF CONGESTIVE HEART FAILURE AND DIABETES MELLITUS.		
AE 001-0906-860013-00		
04-AUG-86	229	PRS. 906-158, 159, 165 AND 200
04-AUG-86	230	SAFETY REPORT
CONTENT:		
PATIENT NO.: 10 (SC)		
PR. 906-85		
AE: DEVELOPED EXCESSIVE HYPOTENSION.		
AE 001-9016-860001-00		
04-AUG-86	230	SAFETY REPORT
CONTENT:		
PATIENT NO.: 19 (WMY)		
PR. 9-007-0		
AE: DEVELOPED A TRANSIENT CEREBRAL ISCHEMIC ATTACK.		
04-AUG-86	230	SAFETY REPORT
CONTENT:		
PATIENT NO.: 19 (WMY)		
PR. 9-003-4		
AE: EXPERIENCED A TRANSIENT CEREBROVASCULAR ACCIDENT WITH DISORIENTATION AND DECREASED RIGHT SIDED STRENGTH.		

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DOC DATE	SER/SUPPL NO	TITLE
15-AUG-86	231	PR. 906-156, 157 AND 192
15-AUG-86	232	PROTOCOL AMENDMENT
CONTENT:		
AMENDMENT NO. 3		
PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 74, 75, 76, 77, 78		
DATE: 3-JUNE-86		
ALLOWS THE DELETION OF THE TREADMILL EXERCISE TEST (ETT) ON THE MORNING OF VISIT 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD) FOR THOSE PATIENTS WHO HAVE COMPLETED TWO PREVIOUS VALID PLACEBO BASELINE ETTS.		
ALLOWS FOR THE SCHEDULING OF VISIT 3, 3 TO 7 DAY AFTER OBTAINING THE SECOND VALID PLACEBO BASELINE ETT.		
15-AUG-86	233	SAFETY REPORT
CONTENT:		
PATIENT NO.: NONE (MIC)		
PR. FRANCE		
AE: EXCESSIVE BLOOD PRESSURE RESPONSE AND HEPATITIS.		
AE 033-9048-860001-00		
15-AUG-86	233	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: NONE (MAG)		
PR. FRANCE		
AE: SYNCOPE AND ARTERIAL COLLAPSE.		
AE 033-0906-860004-00		
22-AUG-86	234	PRS. 906-141, 143, 145, 147, 149, 150, 161, 162, 166, 168, 169, 170, 195
28-AUG-86	235	PR. 906-160 (PAR/47)
28-AUG-86	236	PR. 906-199 (PAR/48)
28-AUG-86	237	PR. 906-183
02-SEP-86	238	SAFETY REPORT
CONTENT:		
PATIENT NO.: NONE ((MAG)		
PR. FRANCE		
AE: SYNCOPE AND ARTERIAL COLLAPSE		
AE 033-0906-860004-01		

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DOC DATE	SER/SUPPL NO	TITLE
02-SEP-86	239	SAFETY REPORT
CONTENT:		
PATIENT NO.: 6 (TES)		
PR. 906-127		
AE: TRANSIENT ISCHEMIC ATTACK.		
NOT DRUG RELATED		
AE 001-0906-860014-00		
02-SEP-86	239	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 6 (ESB)		
PR. 906-133		
AE: DEVELOPED SYNCOPE.		
AE 001-0906-860015-00		
05-SEP-86	240	PR. 906-184
05-SEP-86	241	INFORMATION AMENDMENT
CONTENT:		
RR 764-00606		
AUTHOR: FERRY, J.J. ET AL		
DATE: 6-AUG-86		
"SINGLE DOSE TO ASSESS THE POTENTIAL DRUG-DRUG		
INTERACTION OF QUINAPRIL (CI-906) AND		
HYDROCHLOROTHIAZIDE (CI-570) IN BEAGLE DOGS"		
18-SEP-86	242	PR. 906-186
18-SEP-86	243	INFORMATION AMENDMENT
CONTENT:		
RR MEMO-720-02260		
AUTHOR: PEARSE, S.B. ET AL		
DATE: 9-SEP-86		
"AN UPDATED INTERIM REPORT OF THE DOUBLE-BLIND		
PHASE OF A FIXED-DOSE, PLACEBO-CONTROLLED STUDY		
TO DETERMINE EFFICACY AND SAFETY OF ORALLY		
ADMINISTERED CI-906 IN PATIENTS WITH MILD TO		
MODERATE HYPERTENSION (PROTOCOL 906-11)"		
29-SEP-86	244	SAFETY REPORT
CONTENT:		
PATIENT NO.: 4 (JJT)		
PR. 906-68		
AE: DEATH - PROBABLE MYOCARDIAL INFARCTION.		
NOT DRUG RELATED.		
AE 001-0906-860016-00		

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DOC DATE	SER/SUPPL NO	TITLE
29-SEP-86	245	SAFETY REPORT
CONTENT:		
PATIENT NO.: 14 (ML)		
PR. 906-30		
AE: ELEVATED LIVER ENZYME LEVELS.		
NOT DRUG RELATED.		
AE 001-0906-860017-00		
03-OCT-86	246	PR. 906-187
03-OCT-86	247	PR. 906-185
03-OCT-86	248	PR. 906-229-0
10-OCT-86	249	PR. 906-182
13-OCT-86	250	SAFETY REPORT
CONTENT:		
PATIENT NO.: 16 (AEC)		
PR. 906-82		
AE: DEVELOPED ERTHEMA MULTIFORME.		
AE 001-0906-860002-00		
17-OCT-86	251	PR. 906-216
17-OCT-86	252	PR. 906-218
27-OCT-86	253	PRS. 906-172, 173, 174, 175, 176, 179
05-NOV-86	254	PRS. 906-171, 177, 180
05-NOV-86	255	PRS. 906-196, 197, 198
05-NOV-86	256	PR. 906-235-0
06-NOV-86	257	SAFETY REPORT
CONTENT:		
PATIENT NO.: 1 (FVR)		
PR. 906-133		
AE: ATRIAL FLUTTER.		
AE 001-0906-860018-00		

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11-NOV-86	258	SAFETY REPORT
CONTENT: PATIENT NO.: 5 (DES) PR. 906-120 AE: SEVERE ANGINA ATTACK. AE 001-0906-860019-00		
14-NOV-86	259	PR. 906-204, 205 & 219/PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PRS. 906-204, 205 AND 219 DATE: 7-MAR-86 PROVIDES FOR THE PARTICIPATION OF WOMEN OF CHILDBEARING POTENTIAL. AMENDMENT NO. 2 PRS. 906-204, 205 AND 206 DATE: 10-APR-86 ALLOW ENROLLEMENT OF PATIENTS WITH FEV1 OR FVC. AMENDMENT NO. 3 PRS. 906-204, 205 AND 206 DATE: 3-JUN-86 ALLOWS FOR THE DELETION OF THE TREADMILL EXCERCISE TEST (ETT) ON THE MORNING OF VISIT 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD)		
14-NOV-86	260	PR. 906-226 CENTERS 1 AND 5
21-NOV-86	261	PR. 906-233 CENTERS 2 AND 4/PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PRS. 906-311 CENTERS 2 AND 4 DATE: 7-MAR-86 PROVIDES FOR THE PARTICIPATION OF WOMEN OF CHILDBEARING POTENTIAL. AMENDMENT NO. 2 PRS. 906-311 CENTERS 2 AND 4 DATE: 10-APR-86 ALLOWS ENROLLMENT OF PATIENTS WITH FEV1 OR FVC. AMENDMENT NO. 3 PRS. 906-311 CENTERS 2 AND 4 DATE: 3-JUN-86 ALLOWS FOR THE DELETION OF THE TREADMILL EXCERCISE TEST (ETT) ON THE MORNING OF VISIT 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD).		

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21-NOV-86	262	PR. 906-226 CENTERS 8 AND 10
21-NOV-86	263	PRS. 906-226 CENTERS 11 & 12 - PRS. 906-277 CENTERS 11 & 12
02-DEC-86	264	PR. 906-234-0
02-DEC-86	265	PRS. 906-226 CENTERS 6 AND 7
02-DEC-86	266	INFORMATION AMENDMENT CONTENT: RR 740-02001 AUTHOR: KRAUSE, B. ET AL DATE: 14-NOV-86 "THE EFFECT OF QUINAPRIL ON PLASMA LIPID CONCENTRATION IN NORMAL RAT: COMPARISON OF REFERENCE ACE INHIBITORS"
09-DEC-86	267	PRS. 906-231 CENTERS 1, 2, 4, 6, 8, 9, 10 AND 11
16-DEC-86	268	ANNUAL REPORT CONTENT: ISSUED DATE: 16-DEC-86
16-DEC-86	269	PR. 906-231-5
16-DEC-86	270	PR. 906-230-0
16-DEC-86	271	INFORMATION AMENDMENT CONTENT: RR MEMO-720-02273 AUTHOR: PEARSE, S.B. ET AL DATE: 12-DEC-86 "AN INTERIM REPORT OF THE DOUBLE-BLIND PHASE OF A FIXED-DOSE, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED CI-906 IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-11)"
16-DEC-86	272	INFORMATION AMENDMENT CONTENT: RR MEMO-724-00070 AUTHOR: FRANK, G. DATE: 8-DEC-86 "THE ACUTE HEMODYNAMIC EFFECTS OF QUINAPRIL, A NEW NON-SULFHYDRYL ANGIOTENSIN CONVERTING ENZYME INHIBITOR, IN PATIENTS WITH SEVERE CONGESTIVE CARDIAC FAILURE (PROTOCOL 906-61)"

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DOC DATE	SER/SUPPL NO	TITLE
16-DEC-86	273	INFORMATION AMENDMENT
CONTENT: RR 764-00652 AUTHOR: FERRY, J.J. ET AL DATE: 12-NOV-86 "BIOAVAILABILITY AND PHARMACOKINETICS OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING SINGLE ORAL AND INTRAVENOUS QUINAPRIL AND CI-928 DOSES ADMINISTERED TO BEAGLE DOGS"		
22-DEC-86	274	SAFETY REPORT
CONTENT: PATIENT NO.: 9 (JG) PR. 906-120 AE: DEVELOPED FACIAL SWELLING, RASH, DIZZINESS AND HEADACHES. NOT DRUG RELATED. AE 001-9999-8600004-00		
30-DEC-86	275	PR. 906-231 CENTERS 3, 7 AND 12
06-JAN-87	276	PR. 906-226 CENTERS 2 AND 4
06-JAN-87	277	PR. 906-227-2
13-JAN-87	278	PR. 906-226-3
13-JAN-87	279	PR. 906-227-3
23-JAN-87	280	PR. 906-226-13
23-JAN-87	281	PR. 906-227-13
23-JAN-87	282	IB UPDATE
CONTENT: DATE: 12-DEC-86 RR X-720-02277 AUTHOR: FRANK, G. ET AL "INVESTIGATOR'S BROCHURE: QUINAPRIL HYDROCHLORIDE (CI-906)"		

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30-JAN-87	283	PROTOCOL ADDENDUM
CONTENT:		
ADDENDUM NO.: NONE		
PR. 906-266		
DATE: 19-JAN-87		
REPLACE THE CAPSULE WITH THE TABLET FORMULATION.		
10-FEB-87	284	SAFETY REPORT
CONTENT:		
PATIENT NO.: 2 (DJ)		
PR. 906-72		
AE: DEATH - PNEUMONIA AND SEPTIC SHOCK.		
DRUG RELATED.		
AE 001-0906-870001-00		
10-FEB-87	285	PR. 906-239-0
10-FEB-87	286	INFORMATION AMENDMENT
CONTENT:		
RR MEMO-710-00354		
AUTHOR: ELLIS, J.E. ET AL		
DATE: 14-JAN-87		
"CI-906, BULK DRUG SUBSTANCE: REVISED		
MANUFACTURING AND ANALYTICAL SPECIFICATIONS FOR		
IND FILING"		
17-FEB-87	287	PROTOCOL ADDENDUM
CONTENT:		
ADDENDUM NO.: NONE		
PR. 906-226		
REVISED PAGES 6 (SECTION B5), 7 (SECTION C9),		
16 (SECTION E), 8 (SECTION D), 7 (SECTION C2),		
7 (SECTION C5), 12 (SECTION 3.6), 13 (SECTION		
2.4), 14 (SECTION 3), 14 (SECTION 4.6), 15		
(SECTION 5(C)), 9 (SECTION V.A1), 15 (SECTION 6		
(B)), 19 (SECTION B2), 5, 11, 16 (SECTION VI,A),		
17 (B), 17 (B1), 17 (B3), 17 (B2) AND 6 (SECTION		
IV,A)		
INCLUDED A REVISED COPY OF THE PROTOCOL WITH		
THE ABOVE MENTIONED REVISIONS.		
17-FEB-87	288	PR. 906-226-9
17-FEB-87	289	PR. 906-227 CENTERS 8, 9 AND 10

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24-FEB-87	290	PR. 906-226-14
24-FEB-87	291	PR. 906-227 CENTERS 4 AND 14
24-FEB-87	292	PR. 906-249-0
04-MAR-87 CONTENT:	293	LETTER RE: MANUFACTURING AND CONTROLS LETTER TO: DIVISION OF CARDIO-RENAL RR X-969-00022 RE: UPDATED DATA FOR 0.0625, 1.0, 1.25, 2.5, 5, 10, 20 AND 40 MG CAPSULES; 40 MG CONTROLLED RELEASE CAPSULES; AND 1.25, 2.5, 5, 10, 20 AND 40 MG TABLETS.
04-MAR-87 CONTENT:	294	SAFETY REPORT PATIENT NO.: 1 (WES) PR. 906-75 AE: DEATH AE 001-0906-870002-00
04-MAR-87 CONTENT:	295	PROTOCOL AMENDMENT AMENDMENT NO. 3 PR. 906-79 DATE: 3-JUN-86 ALLOWS FOR THE DELETION OF THE TREADMILL EXERCISE TEST (ETT) ON THE MORNING OF VIST 3 (BEGINNING OF THE DOUBLE-BLIND PERIOD).
04-MAR-87 CONTENT:	296	INFORMATION AMENDMENT RR 764-00663 AUTHOR: FERRY, J.J. ET AL DATE: 5-JAN-87 "EFFECT OF CIMETIDINE ON SINGLE DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS: PROTOCOL 906-113"
09-MAR-87 CONTENT:	297	SAFETY REPORT PATIENT NO.: 4 (KIN) PR. 906-66 AE: DEATH - ARRHYTHMIA PATIENT'S NO. WAS INADVERTENTLY SUBMITTED AS 2. FOLLOW-UP REPORT - SERIAL #297 AE 001-0906-860012-01

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DOC DATE	SER/SUPPL NO	TITLE
09-MAR-87	298	PR. 906-237-0
09-MAR-87	299	INFORMATION AMENDMENT
CONTENT: RR: 764-00635 AUTHOR: FERRY, J.J. ET AL DATE: 14-JAN-87 "CLINICAL BIOEQUIVALENCE STUDY COMPARING THREE QUINAPRIL CAPSULES AND A QUINAPRIL ORAL SOLUTION. PROTOCOL 906-99"		
11-MAR-87	300	SAFETY REPORT
CONTENT: PATIENT NO.: 23 (AWT) PR. 906-46 AE: DEVELOPED ANEMIA. NOT DRUG RELATED. AE 001-0906-870003-00		
11-MAR-87	301	INFORMATION AMENDMENT
CONTENT: REVISED PAGE FOR PRL. 906-249-0 PG. 3 PAGE WAS MISSING WHEN THE PROTOCOL WAS ORGINALLY FILED.		
12-MAR-87	302	SAFETY REPORT
CONTENT: PATIENT NO.: 1 (WES) PR. 906-75 AE: DEATH NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #294 AE 001-0906-870002-01		
12-MAR-87	303	SAFETY REPORT
CONTENT: PATIENT NO.: 9 (RGB) PR. 906-122 AE: DEATH AE 001-0906-870004-00		
12-MAR-87	304	SAFETY REPORT
CONTENT: PATIENT NO.: 13 (KES) PR. 906-45 AE: EXPERIENCED A MYOCARDIAL INFARCTION. AE 001-0906-870005-00		

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DOC DATE	SER/SUPPL NO	TITLE
12-MAR-87	305	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-230-0 CHANGES THE TREATMENT FROM A SINGLE 40 MG CAPSULE TO TWO 20 MG CAPSULES.
12-MAR-87	306	INFORMATION AMENDMENT
CONTENT:		RR 764-00740 AUTHOR: FERRY, J.J. ET AL DATE: 17-FEB-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS, A QUINAPRIL CAPSULE FORMULATION, AND A QUINAPRIL ORAL SOLUTION, PROTOCOL 906-202"
16-MAR-87	307	SAFETY REPORT
CONTENT:		PATIENT NO.: 5 (JAB) PR. 906-96 AE: HAD CORNARY ARTERY BYPASS SURGERY. NOT DRUG RELATED. AE 001-0906-870006-00
16-MAR-87	308	SAFETY REPORT
CONTENT:		PATIENT NO.: 6 (DK) PR. 906-138 AE: HAD A MASTECTOMY. NOT DRUG RELATED. AE 001-0906-870007-00
16-MAR-87	309	SAFETY REPORT
CONTENT:		PATIENT NO.: 8 (TJK) PR. 906-77 AE: EXPERIENCED A COMPLETE HEART BLOCK. AE 001-0906-870008-00
16-MAR-87	310	PR. 906-226 CENTERS 17 AND 18
16-MAR-87	311	PR. 906-226-18

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DOC DATE	SER/SUPPL NO	TITLE
19-MAR-87	312	SAFETY REPORT
CONTENT: PATIENT NO.: 24 (WKH) PR. 906-33 AE: LOSS OF CONSCIOUSNESS. AE 001-0906-870009-00		
19-MAR-87	313	PR. 906-242-07
19-MAR-87	314	INFORMATION AMENDMENT
CONTENT: RR X-720-02147 AUTHOR: FRANK, G.J. ET AL DATE: 12-FEB-87 "OVERALL REPORT OF A MULTICENTER, FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED, SIX-WEEK STUDY OF THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION"		
26-MAR-87	315	PR. 906-183X
26-MAR-87	316	PR. 906-226-19
26-MAR-87	317	PR. 906-227-19
26-MAR-87	318	PRS. 906-228 CENTERS 1,2,3,4,5,7,8,9,10,13,14,18,19,20,22,24
26-MAR-87	319	SAFETY REPORT
CONTENT: PATIENT NO.: 1 PR. 906-218 AE: AN ACUTE MYOCARDIAL INFARCTION. NOT DRUG RELATED. AE 001-9999-8700001-00		
31-MAR-87	320	SAFETY REPORT
CONTENT: PATIENT NO.: 8 (TJK) PR. 906-77 AE: EXPERIENCED A COMPLETE HEART BLOCK. NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #309 AE 001-0906-870008-01		

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DOC DATE	SER/SUPPL NO	TITLE
02-APR-87	321	PRS. 906-238 CENTERS 12, 15, 16, 21, 25, 26
02-APR-87	322	PRS. 906-226 CENTERS 20 AND 21
02-APR-87	323	PR. 906-227-20
02-APR-87	324	SAFETY REPORT
CONTENT:		
PATIENT NO.: 60		
PR. WLI 9-003-0		
AE: MYOCARDIAL INFARCTION 11 DAY AFTER STARTING		
ENALPRIL THERAPY.		
NOT DRUG RELATED.		
AE 033-9048-860002-00		
02-APR-87	324	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 361 (NONE)		
PR. WLI 9-003-4		
AE: BLEEDING TENDENCY.		
DRUG RELATED.		
AE 060-0906-860001-00		
02-APR-87	324	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 45 (NONE)		
PR. WLI 9-030-0		
AE: SUSPECTED MYOCARDIAL INFARCTION.		
NOT DRUG RELATED.		
AE 044-0906-860001-01		
02-APR-87	324	SAFETY REPORT - CONTINUED
CONTENT:		
PATIENT NO.: 24 (NONE)		
PR. 906-11		
AE: CHEST PAIN.		
NOT DRUG RELATED.		
AE 358-0906-87000-00		
03-APR-87	325	SAFETY REPORT
CONTENT:		
PATIENT NO.: 1 (NONE)		
PR. WLI 9-008-1		
AE: PATIENT HAD AN ERYTHEMATOUS ERUPTION AND		
PRURITUS WHICH DEVELOPED WHILE PARTICIPATING		
IN THE STUDY.		
POSSIBLE DRUG RELATED.		
AE 033-0906-860005-00		

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DOC DATE	SER/SUPPL NO	TITLE
06-APR-87	326	SAFETY REPORT
CONTENT: PATIENT NO.: 2 (DJ) PR. 906-72 AE: DEATH - PNEUMONIA AND SEPTIC SHOCK. NOT DRUG RELATED FOLLOW-UP REPORT - SERIAL #248 AE 033-0906-860005-00		
06-APR-87	327	PR. 906-238-23
14-APR-87	328	SAFETY REPORT
CONTENT: PATIENT NO.: 23 (AWT) PR. 906-46 AE: DEVELOPED ANEMIA. NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #300 AE 001-0906-870003-01		
14-APR-87	329	PR. 906-238 CENTERS 11 AND 27
22-APR-87	330	PRS. 906-226-15, 16, 32, 34/ 906-238-22 THRU 30, 32
22-APR-87	331	PR. 906-227 CENTERS 22, 24, 25, 26, 28, 29, 32, 33, 34
22-APR-87	332	SAFETY REPORT
CONTENT: PATIENT NO.: 4 (JJT) PR. 906-68 AE: DEATH - MYOCARDIAL INFARCTION. AE 001-0906-860016-01		
24-APR-87	333	SAFETY REPORT
CONTENT: PATIENT NO.: 3 (RAC) PR. 906-35 AE: HAD AN ACUTE MYOCARDIAL INFARCTION. AE 001-0906-870010-00		
24-APR-87	334	PR. 906-244-0

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DOC DATE	SER/SUPPL NO	TITLE
24-APR-87	335	PR. 906-233-5
01-MAY-87	336	SAFETY REPORT
CONTENT: PATIENT NO.: 8 (TJK) PR. 906-77 AE: EXPERIENCED A COMPLETE HEART BLOCK. NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #309 AE 001-0906-870008-02		
01-MAY-87	337	SAFETY REPORT
CONTENT: PATIENT NO.: 345 (BMA) PR. 9-003-4 AE: DEATH POSSIBLY DRUG RELATED. AE 032-0906-870001-00		
04-MAY-87	338	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 4 PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 75, 77, 78, 79, 204, 205, 216, 218, 219 & 233-2 DATE: 29-DEC-86 PERMITS WEEKLY CLINICAL VISITS TO BE OPTIONAL AT THE INVESTIGATOR'S DISCRETION FOR PATIENTS WHO ARE STABLE. DRUG ASSAY WILL BE REQUIRED AT SPECIFIC DOUBLE- BLIND VISITS.		
12-MAY-87	339	SAFETY REPORT
CONTENT: PATIENT NO.: 5 (BW) PR. 906-67 AE: EXPERIENCED SWELLING OF THE TONGUE. AE 001-0906-870012-00		
12-MAY-87	340	SAFETY REPORT
CONTENT: PATIENT NO.: 1 (CFO) PR. 906-219 AE: DEATH NOT DRUG RELATED. AE 001-0906-870011-00		

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12-MAY-87 341 PROTOCOL AMENDMENT
CONTENT:

AMENDMENT NO. 4
PR. 906-94
DATE: AUG-86
PROVIDES FOR EVALUATION OF QUINAPRIL THERAPY ON
PLASMA LIPIDS AND MONITORS THE EFFICACY OF
QUINAPRIL IN LOW AND NORMAL-RENIN SUBGROUPS.

AMENDMENT NO. 5
PR. 906-94
DATE: 4-MAR-87
PROVIDES FOR HOURLY BLOOD PRESSURE MONITORING.

12-MAY-87 342 PROTOCOL AMENDMENT
CONTENT:

AMENDMENT NO. 3
PR. 906-22
PROVIDES FOR AN ADDITIONAL 12 MONTH CONTINUATION
OF OPEN-LABEL TREATMENT.

19-MAY-87 343 PR. 906-254-0

19-MAY-87 344 PROTOCOL AMENDMENT
CONTENT:

AMENDMENT NO. 5
PRS. 906-63, 64, 65, 66, 67, 68, 69, 72, 73, 75,
77, 78, 79, 204, 205, 216, 218, 219, AND
233-2
DATE: 13-FEB-87
ADDS AN EXCLUSION FOR PATIENTS BASED ON ANA TITER.

19-MAY-87 345 PR. 906-226-35

19-MAY-87 346 PR. 906-227-35

19-MAY-87 347 PR. 906-246 CENTERS 1, 3, 4 AND 5

26-MAY-87 348 SAFETY REPORT
CONTENT:

PATIENT NO.: 16 (SOP)
PR. 906-68
AE: DEATH
NOT DRUG RELATED.
AE 001-0906-870013-00

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26-MAY-87	349	PR. 906-252 CENTERS 1 AND 2
26-MAY-87	350	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-231-1 DATE: 10-FEB-87 ESTABLISHES A MAXIMUM ALLOWABLE RISE IN CREATININE TO A VALUE OF 2.5 MG/DL.		
26-MAY-87	351	INFORMATION AMENDMENT
CONTENT: RR 764-00771 AUTHOR: HORVATH, A.M. ET AL DATE: 13-APR-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS AND A QUINAPRIL CAPSULE FORMULATION, PROTOCOL 906-234"		
26-MAY-87	352	INFORMATION AMENDMENT
CONTENT: RR 720-02331 AUTHOR: IMBARRATO, C. ET AL DATE: 15-MAY-87 "EFFECTS OF ORAL QUINAPRIL ON BLOOD PRESSURE, HEART RATE, AND PULMONARY FUNCTION MEASUREMENTS IN HEALTHY SUBJECTS (PROTOCOL 906-232-0)"		
26-MAY-87	353	INFORMATION AMENDMENT
CONTENT: RR X-720-02185 AUTHOR: FRANK, G.J. ET AL DATE: 8-MAY-87 "OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF ONCE-A-DAY, ORALLY- ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH CHLORTHALIDONE AND WITH CONCOMITANT QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION"		
27-MAY-87	354	SAFETY REPORT
CONTENT: PATIENT NO.: 2 (SJ) PR. 891-151 AE: DEATH - CARDIOMYOPATHY SECONDARY TO CHF. AE 049-0906-870005-00		

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02-JUN-87	355	PR. 906-246-2
02-JUN-87	356	PR. 906-247 CENTERS 2, 3, 4
02-JUN-87	357	PRS. 906-250 CENTERS. 1 AND 2
02-JUN-87	358	INFORMATION AMENDMENT CONTENT: RR 764-00786 AUTHOR: MCNALLY, W. ET AL DATE: 27-APR-87 "WHOLE-BODY AUTORADIOGRAPHIC ANALYSIS OF TISSUE DISTRIBUTION OF 14-C-CI-906 IN RATS"
02-JUN-87	359	INFORMATION AMENDMENT CONTENT: RR 764-00779 AUTHOR: FERRY, J.J. ET AL DATE: 24-APR-87 "SINGLE DOSE PHARMACOKINETIC DRUG-DRUG INTERACTION STUDY OF QUINAPRIL (CI-906) AND HYDROCHLOROTHIAZIDE (CI-570) IN HEALTHY VOLUNTEERS. PROTOCOL 906-221"
02-JUN-87	360	PR. 906-226-31
09-JUN-87	361	PR. 906-251-1
09-JUN-87	362	INFORMATION AMENDMENT CONTENT: RR MEMO-720-02325 AUTHOR: FRANK, G.J. ET AL DATE: 22-MAY-87 "TWENTY-FOUR BLOOD PRESSURE AND HEART RATE RESPONSES TO ONCE-DAILY QUINAPRIL HYDROCHLORIDE (CI-906) MEASURED BY AMBULATORY MONITORING IN HYPERTENSIVE PATIENTS RECEIVING OPEN-LABEL QUINAPRIL (PROTOCOLS 906-33 AND 906-25)"
16-JUN-87	363	PR. 906-251-2
16-JUN-87	364	PR. 906-253-1

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16-JUN-87	365	PR. 906-258-1
18-JUN-87	366	PR. 906-259-0
25-JUN-87	367	PR. 906-250-3
25-JUN-87	368	INFORMATION AMENDMENT
CONTENT: RR 764-007092 AUTHOR: FERRY, J.J. ET AL DATE: 8-JUN-87 "EFFECT OF QUINAPRIL ON THE MULTIPLE DOSE PHARMACOKINETICS OF DIGOXIN IN HEALTHY VOLUNTEERS, PROTOCOL 906-209"		
29-JUN-87	369	SAFETY REPORT
CONTENT: PATIENT NO.: 5 (BW) PR. 906-67 AE: EXPERIENCED SWELLING OF THE TONGUE. POSSIBLY DRUG RELATED. AE 001-0906-870012-01		
07-JUL-87	370	PR. 906-256-0
07-JUL-87	371	PROTOCOL AMENDMENTS
CONTENT: AMENDMENT NO. 2 PRS. 906-114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 125, 126, 127, 128, 129, 131, 132, 133, 134, 136, 137 AND 138 DATE: 25-AUG-86 ALLOWS PEAK (POST DOSE) MONITORING FOR BLOOD PRESSURE AND HEART RATE MEASUREMENTS TO BE OPTIONAL FOR PATIENTS NOT REQUIRING TITRATION OR ADDITION OF HYDROCHLOROTHIAZIDE. AMENDMENT NO. 3 PRS. 906-124 DATE: 25-AUG-86 ALLOWS PEAK (POST DOSE) MONITORING FOR BLOOD PRESSURE AND HEART RATE MEASUREMENTS TO BE OPTIONAL FOR PATIENT NOT REQUIRING TITRATION OR ADDITION OF HYDROCHLOROTHIAZIDE.		

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22-JUL-87	372	INFORMATION AMENDMENT
CONTENT:		REVISED PAGE RR X-720-02277 PG. 5 DATE: 15-JUL-87 CROSS REFERENCE: SERIAL #17
22-JUL-87	373	LETTER RE: PROTOCOL CANCELLATION
CONTENT:		PR. 906-152 RE: CANCELLATION OF PROTOCOL
22-JUL-87	374	PROTOCOL AMENDMENTS
CONTENT:		AMENDMENT NO. 1 PR. 906-30 DATE: 17-JUN-85 PROVIDE FOR ADDITIONAL BLOOD PRESSURE MEASUREMENTS AMENDMENT NO. 2 PRS. 906-30, 32, 41 AND 130 DATE: 20-AUG-85 PROVIDES FOR TWICE A DAY DOSING OF QUINAPRIL HCL (CI-906) IN THE OPEN-LABEL PHASE OF PROTOCOL 906, CHLORTHALIDONE IN MILD TO MODERATE HYPERTENSIVE PATIENTS. AMENDMENT NO. 3 PRS. 906-30, 31, 34, 36, 37, 38 AND 41 DATE: 31-AUG-86 PROVIDES FOR AN ADDITIONAL 12 MONTH CONTINUATION OF THE LONG-TERM, OPEN LABEL PERIOD OF TREATMENT.
22-JUL-87	374	PROTOCOL AMENDMENTS - CONTINUED
CONTENT:		AMENDMENT NO. 4 PR. 906-33 DATE: 20-AUG-85 PROVIDES FOR TWICE A DAY DOSING OF QUINAPRIL HYDROCHLORIDE (CI-906) IN THE OPEN-LABEL PHASE OF PROTOCOL 906, CHLORTHALIDONE IN MILD TO MODERATE HYPERTENSIVE PATIENTS.
22-JUL-87	375	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-250-1 DATE: NONE PROVIDES FOR ADDITIONAL BLOOD PRESSURE MEASUREMENT AND A CLINICAL LABORATORY, ELECTROCARDIOGRAM, AND PHYSICAL EXAMINATION.

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22-JUL-87	376	INFORMATION AMENDMENT
CONTENT:		
		RR 250-01471 AUTHOR: ROGERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL- HYDROCHLOROTHIAZIDE COMBINATION) IN MICE"
		RR 250-01484 AUTHOR: ROGERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL- HYDROCHLOROTHIAZIDE COMBINATION) IN RATS"
22-JUL-87	377	INFORMATION AMENDMENT
CONTENT:		
		RR 764-00808 AUTHOR: FERRY, J.J. ET AL DATE: 26-JUN-87 "SINGLE-DOSE, BIOEQUIVALENCE STUDY COMPARING QUINAPRIL 2.5-MG MARKET-IMAGE TABLETS AND QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS, PROTOCOL 906-239"
		RR 764-00820 AUTHOR: HORVATH, A.M. ET AL DATE: 26-JUN-87 "EFFECT OF MULTIPLE-DOSE PROPRANOLOL ADMINISTRATION ON SINGLE-DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS. PROTOCOL 906-229"
22-JUL-87	378	INFORMATION AMENDMENT
CONTENT:		
		RR MEMO-720-02335 AUTHOR: FRANK, G.J. ET AL DATE: 1-JUN-87 "GLOBAL RESPONSE ADDENDUM TO QUINAPRIL (CI-906) FIXED-DOSE MULTICENTER STUDY (RR-X-720-02147)"
31-JUL-87	379	LETTER RE: REQUEST FOR MEETING
CONTENT:		
		LETTER TO: LIPICKY, J., M.D. RE: REQUESTING A MEETING CONCERNING DEVELOPMENT OF A COMBINATION DRUG PRODUCT CONSISTING OF QUINAPRIL AND HYDROCHLOROTHIAZIDE.

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DOC DATE	SER/SUPPL NO	TITLE
31-JUL-87	380	PR. 906-255-0
31-JUL-87	381	INFORMATION AMENDMENT
CONTENT: RR 724-00072 AUTHOR: FRANK, G.J. ET AL DATE: 17-JUL-87 "REPORT OF A SINGLE RISING-DOSE STUDY AND A MULTIPLE-DOSE EXTENDED-TREATMENT STUDY CONDUCTED TO ASSESS THE SAFETY, PHARMACOLOGICAL ACTIVITY, ADMINISTERED TO PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOLS 906-7 AND 906-9)"		
31-JUL-87	382	INFORMATION AMENDMENT
CONTENT: REVISED PAGE RR 745-00441 PG. 11 DATE: 21-JUL-87		
31-JUL-87	383	PROTOCOL AMENDMENTS
CONTENT: AMENDMENT NO. 1 PR. 906-226-2 DATE: 30-APR-87 PROVIDES FOR THE RADIONUCLIDE ASSESSMENT TO BE MEASURED AT BOTH REST AND EXERCISE AND SCHEDULE AND ADDITIONAL MORE COMPREHENSIVE ASSESSMENT TO QUALITY OF LIFE TO BE PERFORMED AT THE LAST VISIT AMENDMENT NO. 2 PR. 906-226-5 DATE: 12-MAY-87 THE DOUBLE-BLIND MEDICATION WILL NOT BE DISPENSED AT VISIT 13 - OPEN LABEL MEDICATION WILL BE DISPENSED.		
31-JUL-87	384	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 6 PRS. 906-77, 78, 205, 218 AND 233-2 DATE: 10-JUN-87 ADDS AN EVALUATION OF HEMODYNAMIC FUNCTION AT THE END OF ONE YEAR OF OPEN-LABEL AND ALSO INCREASES THE DURATION OF THE OPEN-LABEL PHASE TO 24 MONTHS.		

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01-SEP-87	385	ANNUAL REPORT
CONTENT:		CUTOFF DATE: 31-JUL-87
01-SEP-87	386	INFORMATION AMENDMENT
CONTENT:		REVISED PAGE RR X 720-02277 PG. 5 DATE: 17-AUG-87
01-SEP-87	387	INFORMATION AMENDMENT
CONTENT:		RR X-720-02327 AUTHOR: FRANK, G.J. ET AL DATE: 24-AUG-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-DAILY (BID) AND ONCE-DAILY (QD) DOSES OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION"
10-SEP-87	388	LETTER RE: CONFIRMATION OF MEETING
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: CONFIRMING MEETING WITH FDA ON 6-OCT-87 AT 10:00 AM TO DISCUSS QUINAPRIL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE CLINICAL AND PRE-CLINICAL TOXICOLOGICAL PROGRAMS.
10-SEP-87	389	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-249-0 ADDS A SECOND OBJECTIVE TO THE STUDY: TO ASSESS THE INFLUENCE OF QUINAPRIL ON HEPATIC DRUG OXIDIZING CAPACITY IN MAN.
18-SEP-87	390	PR. 906-257-0
18-SEP-87	391	INFORMATION AMENDMENT
CONTENT:		RR 250-01507 AUTHOR: ROGERS, S.C. ET AL DATE: 18-AUG-87 "13 WEEK DAILY REPEATED DOSE ORAL TOXICITY STUDY OF CI-955 IN RATS"

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DOC DATE	SER/SUPPL NO	TITLE
02-OCT-87	392	PR. 906-244-0
02-OCT-87	393	INFORMATION AMENDMENT
CONTENT:		
RR 745-01155		
AUTHOR: MCGUIRE, E.J.		
DATE: 9-SEP-87		
"TWO-YEAR CARCINOGENICTY STUDY OF CI-906 IN MICE"		
19-OCT-87	394	INFORMATION AMENDMENT
CONTENT:		
RR 764-00856		
AUTHOR: OLSON, S.C. ET AL		
DATE: 2-SEP-87		
"CLINICAL DOSE PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING 2.5 MG TO 80 MG SINGLE CAPSULES DOSES OF QUINAPRIL, PROTOCOL 906-191"		
RR 764-00870		
AUTHOR: OLSON, S.C. ET AL		
DATE: 6-OCT-87		
"EFFECT OF QUINAPRIL ON WARFARIN-INDUCTED REDUCTION IN PROTHROMBIN COMPLEX ACTIVITY IN HEALTHY SUBJECTS - PROTOCOL 906-235"		
19-OCT-87	395	INFORMATION AMENDMENT
CONTENT:		
RR 745-01156		
AUTHOR: KRISHNA, G. ET AL		
DATE: 14-SEPT-87		
"MOUSE MICRONUCLEUS STUDY OF CI-906"		
RR 745-01168		
AUTHOR: KROPKO, M.L. ET AL		
DATE: 14-SEP-87		
"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906 IN V79 CHINESE HAMSTER LUNG CELLS"		
19-OCT-87	396	INFORMATION AMENDMENT
CONTENT:		
RR 250-01510		
AUTHOR: ROGERS, S.R. ET AL		
DATE: 10-SEP-87		
"13 WEEK ORAL TOXICITY STUDY OF CI-955 IN BEAGLE DOGS"		

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29-OCT-87 CONTENT:	397	LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROL LETTER TO: DIVISION OF CARDIO-RENAL RR 710-00431 RE: UPDATED CHEMISTRY, MANUFACTURING AND CONTROLS DATA.
29-OCT-87	398	PR. 906-241 CENTERS 3, 4, 5, 6, 7, 8 AND 17
29-OCT-87 CONTENT:	398	NEW SUB-INVESTIGATOR PR. 906-250-2 LLOYD, DOUGLAS, M.D.
05-NOV-87	399	PR. 906-241 CENTERS 2, 9, 10, 11, 12, 21, 24, 27 AND 30
05-NOV-87 CONTENT:	400	PROTOCOL AMENDMENT AMENDMENT NO. 6 PRS. 906-64, 65, 66, 67, 68, 72, 73, 75, 79, 204, AND 233-5 DATE: 13-MAR-87 ADDS AN EVALUATION OF HEMODYNAMIC FUNCTION AT THE END OF ONE YEAR OF OPEN LABEL AND ALSO INCREASES THE DURATION OF THE OPEN LABEL PHASE TO 24 MONTHS.
12-NOV-87 CONTENT:	401	PRS. 906-241-18, -227 CENTERS 30 & 31, -253-2/PR. AMENDMENT AMENDMENT NO. 1 PR. 906-253-1 DATE: NONE VASODILATORS USED IN THE TREATMENT OF HYPERTENSION ARE FORBIDDEN AND THAT RENAL FUNCTION EVALUATION WILL BE CARRIED OUT AT THE 4TH WEEK OF ACTIVE TREATMENT.
19-NOV-87 CONTENT:	402	INFORMATION AMENDMENT/PROTOCOL AMENDMENT/ADDENDUM REVISED PAGE RR 745-00479 PG. 13 DATE: 5-NOV-87 REVISED PAGE RR 745-00608 PG. 2 DATE: 5-NOV-87 REVISED PAGE RR 745-00749 PG. 2 DATE: 5-11-87 AMENDMENT NO. 4 PR. 906-71

DATE: 10-JUN-87

ADDS AN EVALUATION OF HEMODYNAMIC FUNCTION AT THE
END OF ONE YEAR OF OPEN LABEL AND ALSO INCREASES
THE DURATION OF THE OPEN LABEL PHASE TO 24
MONTHS.

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19-NOV-87 CONTENT:	402	INFORMATION AMENDMENT/PROTOCOL AMENDMENT/ADDENDUM-CONTINUED ADDENDUM NO. 1 PR. 906-258-1 DATE: NONE VASODILATORS USED IN THE TREATMENT OF HYPERTENSION ARE FORBIDDEN AND THAT RENAL FUNCTION EVALUATION WILL BE CARRIED OUT AT THE 4TH WEEK OF ACTIVE TREATMENT.
19-NOV-87	403	PR. 906-241 CENTERS 16, 20 AND 28, PR. 906-258-4
19-NOV-87 CONTENT:	404	INFORMATION AMENDMENT RR 720-02337 AUTHOR: FRANK, G.J. ET AL DATE: 6-NOV-87 "A 28-WEEK PARALLEL GROUP DOUBLE-BLIND DOSE- RANGING STUDY OF QUINAPRIL (CI-906) IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL 9-007)" RR 724-00079 AUTHOR: FRANK, G.J. ET AL DATE: 6-NOV-87 "A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY, PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOL 906-61 (P.254) "
30-NOV-87 CONTENT:	405	INFORMATION AMENDMENT RR 250-01515 AUTHOR: MACALLUM, G.E. ET AL DATE: 9-NOV-87 "ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906 (PD 109452-2) IN RATS" RR 250-01516 AUTHOR: MACALLUM, G.E. ET AL DATE: 9-NOV-87 "ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906 (PD 109452-2) IN MICE"
30-NOV-87 CONTENT:	406	INFORMATION AMENDMENT RR MEMO-720-02350 AUTHOR: FRANK, G.J. ET AL DATE: 12-NOV-87 "REPORT OF 24-HOUR BLOOD PRESSURE MONITORING AND ASSESSMENT OF URINARY PROTEIN EXCRETION DURING A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE EFFICACY OF ONCE- OR TWICE-DAILY QUINAPRIL HYDROCHLORIDE WITH THAT OF Captopril

ADMINISTERED THREE TIMES A DAY (906-124)
(SUPPLEMENT TO RR-X-720-02346) "

RR 724-00082

AUTHOR: FRANK, G.J. ET AL

DATE: 19-NOV-87

"A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY
AND PHARMACOLOGICAL ACTIVITY OF ORALLY
ADMINISTERED QUINAPRIL IN PATIENTS WITH
CONGESTIVE HEART FAILURE (PROTOCOL 906-50
(P.239) "

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30-NOV-87 406 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR MEMO-764-00857

AUTHOR: FRANK, G.J. ET AL

DATE: 19-NOV-87

"SINGLE AND MULTIPLE ORAL DOSE PHARMACOKINETICS
OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE
(CI-928) IN YOUNG AND ELDERLY VOLUNTEERS,
PROTOCOL 906-223"

RR 764-00861

AUTHOR: ALSON, S.C. ET AL

DATE: 29-OCT-87

"SINGLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN
PATIENTS WITH HEPATIC IMPAIRMENT SECONDARY TO
ALCOHOL-INDUCED CIRRHOSIS - PROTOCOL 9-032-0"

30-NOV-87 406 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR 764-000867

AUTHOR: OLSON, S.C. ET AL

DATE: 2-OCT-87

"PHARMACOKINETIC DISPOSITION OF ¹⁴C-QUINAPRIL AND
ITS ACTIVE METABOLITE, CI-928, AFTER SINGLE AND
MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY
VOLUNTEERS, PROTOCOL 906-60"

RR 764-000872

AUTHOR: OLSON, S.C. ET AL

DATE: 2-OCT-87

"EFFECT OF MAGNESIUM-CONTAINING QUINAPRIL TABLETS
ON THE SINGLE-DOSE PHARMACOKINETICS OF
TETRACYCLINE IN HEALTHY VOLUNTEERS, PROTOCOL
906-237"

30-NOV-87 407 INFORMATION AMENDMENT
CONTENT:

RR 4301-00015

AUTHOR: BAKOVIC-ALT, R. ET AL

DATE: 18-AUG-87

"REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO
CONTROLLED, 12-WEEK STUDY DETERMINING THE
EFFICACY AND SAFETY OF TWICE-A-DAY, ORALLY
ADMINISTERED QUINAPRIL 5 MG, 10 MG AND 20 MG IN
THE TREATMENT OF CONGESTIVE HEART FAILURE
(CT 891-140)"

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30-NOV-87	408	INFORMATION AMENDMENT
CONTENT:		
RR MEMO-4301-00032		
AUTHOR: BAKOVIC-ALT, R. ET AL		
DATE: 11-SEP-87		
"REPORT OF A ONE-YEAR OPEN-LABEL MULTICENTER STUDY FOLLOWING A 12-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF ORAL ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH CONGESTIVE HEART FAILURE (INTERIM ANALYSIS, CT 891-140 FF)"		
01-DEC-87	409	MINUTES OF FDA MEETING
CONTENT:		
DATE: 6-OCT-87		
DISCUSSED THE PHASE 2/3 CLINICAL PROGRAM AND NDA FOR THE COMBINATION OF QUINAPRIL (CI-906 AND HYDROCHLOROTHIAZIDE TO BE USED AS ANTIHYPERTENSIVE THERAPY.		
15-DEC-87	410	INFORMATION AMENDMENT
CONTENT:		
RR 745-01173		
AUTHOR: ANDERSON, JA. ET AL		
DATE: 13-NOV-87		
"104-WEEK CARCINOGEN BIOASSAY WITH CI-906 IN RATS"		
15-DEC-87	411	INFORMATION AMENDMENT
CONTENT:		
RR 720-02364		
AUTHOR: FRANK, G.J. ET AL		
DATE: 17-NOV-87		
INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED CI-906 IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-12, 906-13 AND 905-15 THRU 906-22)"		
15-DEC-87	412	INFORMATION AMENDMENT
CONTENT:		
RR 740-02311		
AUTHOR: DAVIS, R.E.		
DATE: 3-DEC-87		
"EFFECT OF PD 109452 (CI-906), AND ANGIOTENSION CONVERTING ENZYME INHIBITOR (ACE) ON BODY TEMPERATURE AND SURVIVAL TIME UNDER NORMOBARIC HYPOXIA IN MICE"		
RR 740-02312		
AUTHOR: DAVIS, R.E.		
DATE: 3-DEC-87		
"EFFECT OF CI-906 (PD 109452), AND ANGIOTENSION		

ALTERNATION PERFORMANCE IN RATS"

REVISED PAGES RR 745-01168

PGS. 3, 9, 10, 159, 163, 182, 184 AND 186

DATE: 24-NOV-87

CROSS REFERENCE: 395

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15-DEC-87	413	PR. 906-241 CENTERS 13, 14 AND 15
22-DEC-87	414	INFORMATION AMENDMENT
CONTENT:		
RR 720-02334 AUTHOR: FRANK, G.J. ET AL DATE: 25-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, PLACEBO-CONTROLLED STUDY TO DETERMINE THE COMPARATIVE EFFICACY AND SAFETY OF ORALLY-ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906), CHLORTHALIDONE, AND QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (RR X-720-02185) (PROTOCOLS 906-30 TO 38, -41 TO 46)"		
22-DEC-87	415	INFORMATION AMEDMENT
CONTENT:		
RR X-720-02318 AUTHOR: FRANK, G.J. ET AL DATE: 19-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 906-86, 906-89 TO 906-91, 906-93, 906-95, 906-96)"		
22-DEC-87	416	PRS. 906-258-03, 906-241-14X, 906-241-32
22-DEC-87	417	INFORMATION AMENDMENT
CONTENT:		
RR 720-02369 AUTHOR: FRANK, G.J. ET AL DATE: 24-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) TO ORALLY ADMINISTERED CAPTOPRIAL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-114 TO 906-131, 906-133, 906-134, 906-137, 906-138)"		
22-DEC-87	418	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGE RR 764-00870 PG. 6/7 DATE: 9-NOV-87 CROSS REFERENCE: SERIAL #394 RR 764-00916 AUTHOR: MICHNIEWICZ, B. ET AL DATE: 10 OCT 87		

"METABOLIC DISPOSITION OF ¹⁴QUINAPRIL IN RATS"

RR 764-00917

AUTHOR: MICHNIEWICZ, B. ET AL.

DATE: 30-NOV-87

"CHARACTERIZATION OF QUINAPRIL METABOLITES IN
URINE OF MAN AND DOG FOLLOWING ADMINISTRATION OF
¹⁴QUINAPRIL"

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29-DEC-87 419 INFORMATION AMENDMENT
CONTENT:

RR X-720-02346
AUTHOR: FRANK, G.J. ET AL
DATE: 11-DEC-87
"A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED,
12-WEEK STUDY TO COMPARE THE EFFICACY AND SAFETY
OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE
(CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN
PATIENTS WITH MILD TO MODERATE ESSENTIAL
HYPERTENSION (PROTOCOL 906-114 TO 906-131,
906-133, 906-124, 906-136 TO 906-138)"

29-DEC-87 420 INFORMATION AMENDMENT
CONTENT:

REVISED PAGES RR X-720-02185
COMPLETE REPORT
DATE: 4-DEC-87
CROSS REFERENCE: SERIAL #353

05-JAN-88 421 INFORMATION AMENDMENT
CONTENT:

RR 764-00887
AUTHOR: HORVATH, A.M. ET AL
DATE: 2-NOV-87
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING
QUINAPRIL 5- AND 40-MG MARKET-IMAGE TABLETS AND
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS -
PROTOCOL 906-230"

RR MEMO-764-00915
AUTHOR: OLSON, S.C. ET AL
DATE: 20-NOV-87
"MULTIPLE ORAL DOSE PHARMACOKINETIC OF QUINAPRIL
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN
RENAL FAILURE - PROTOCOL 906-AE INTERIM ANALYSIS"

05-JAN-88 422 INFORMATION AMENDMENT
CONTENT:

RR 720-02349
AUTHOR: FRANK, G. ET AL
DATE: 20-NOV-87
"REPORT OF A COMPARATIVE PHARMACOKINETIC STUDY OF
ONCE-DAILY ORALLY ADMINISTERED QUINAPRIL
HYDROCHLORIDE (CI-906) IN YOUNG SUBJECTS AND
ELDERLY PATIENTS WITH MILD TO MODERATE
HYPERTENSION (906-223)"

RR 724-00081
AUTHOR: FRANK G.J., ET AL
DATE: 30-NOV-87
"A 16-WEEK, MULTIPLE-DOSE STUDY OF THE SAFETY,
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF
ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH
CONGESTIVE HEART FAILURE (PROTOCOL 906-62
(P. 255))"

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05-JAN-88	423	INFORMATION AMENDMENT
CONTENT:		
RR X-720-02345		
AUTHOR: FRANK, G.J.		
DATE: 25-NOV-87		
"INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF TWICE- DAILY (BID) AND ONCE-DAILY (QD) ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-11, 906-48, 906-49 AND 906-52 TO 906-59)"		
12-JAN-88	424	INFORMATION AMENDMENT
CONTENT:		
RR 720-02338		
AUTHOR: FRANK, G.J. ET AL		
DATE: 10-DEC-87		
"A MULTICENTER, 28-WEEK, PARALLEL GROUP, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING STUDY OF QUINAPRIL (CI-906) VERSUS ENALPRIL IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL WLI-9-003-4)"		
12-JAN-88	425	INFORMATION AMENDMENT
CONTENT:		
RR 4301-00023		
AUTHORS: WOELFING, A. LILIENTHAL, H.		
DATE: 11-SEP-87		
"REPORT OF A MULTICENTER, DOUBLE-BLIND, 28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE- A-DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH ENALAPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (CT 890-200)"		
12-JAN-88	426	INFORMATION AMENDMENT
CONTENT:		
RR: 740-02345		
AUTHORS: STEFFEN, R.P. ELDON, C.M.		
DATE: 11-DEC-87		
"EFFECT OF ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS ON RENAL AND PERIPHERAL HEMODYNAMICS AND URINE OUTPUT IN ANESTHETIZED DOG"		
RR 740-02378		
AUTHOR: SINGER, R. ET AL		
DATE: 16-DEC-87		
"EFFECTS OF QUINAPRIL ON BLOOD PRESSURE AND HEART RATE IN DIURETIC-TREATED RENAL HYPERTENSIVE DOGS"		

REVISED PAGE RR MEMO-764-00916

PG. 2/3

DATE: 23/DEC-87

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12-JAN-88 427 PR 906-241-19/INFORMATION AMENDMENT
CONTENT:

REVISED PAGES RR 724-00039
PGS. 6/7 AND 8/9

RR 724-00083

AUTHOR: FRANK, G.J. ET AL

DATE: 18-DEC-87

"A 16-WEEK, MULTIPLE-DOSE STUDY OF THE SAFETY,
PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF
ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH
CONGESTIVE HEART FAILURE (PROTOCOL 906-51 P.240)"

19-JAN-88 428 INFORMATION AMENDMENT
CONTENT:

REVISED PAGE RR 764-00867
PG. 2/3
DATE: 5-JAN-88

RR MEMO-745-01206

AUTHOR: ANDREWS, L.K.

DATE: 22-DEC-87

"TWO-YEAR CARCINOGENICITY STUDY OF CI-906 IN MICE:
A REVIEW OF HISTOPATHOLOGIC CHANGES IN THE
KIDNEY"

19-JAN-88 429 INFORMATION AMENDMENT
CONTENT:

RR 740-02354

AUTHORS: WEISHAAR, R.
ESSENBERG, A.

DATE: 4-JAN-88

"EFFECT OF PD 109489-2K AND REFERENCE AGENTS ON
THE ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02355

AUTHORS: WEISHAAR, R.E.
ESSENBERG, A.D.

DATE: 4-JAN-88

"EFFECT OF PD 109478-2 AND REFERENCE AGENTS ON THE
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02356

AUTHOR: WEISHAAR, R.E.
ESSENBERG, A.D.

DATE: 4-JAN-88

"EFFECT OF PD 126130 AND REFERENCE AGENTS ON THE
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

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19-JAN-88 429 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR 740-02357

AUTHORS: WEISHAAR, R.E.
ESSENBERG, A.D.

DATE: 4-JAN-88

"EFFECT OF PD 118854 AND REFERENCE AGENTS ON THE
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

19-JAN-88 430 INFORMATION AMENDMENT
CONTENT:

RR 4301-00030

AUTHORS: FRIEDRICH, R.
SAUERMAN, W.

DATE: 31-AUG-87

"REPORT OF A DOUBLE-BLIND, FIXED-DOSE, PLACEBO-
CONTROLLED, 2-WEEK STUDY OF THE EFFICACY AND
SAFETY OF ORALLY ADMINISTERED QUINAPRIL
HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO
MODERATE HYPERTENSION UNDER EXERCISE STRESS TEST
CONDITIONS"

19-JAN-88 431 INFORMATION AMENDMENT
CONTENT:

RR X-720-02367

AUTHOR: FRANK, G.J. ET AL
DATE: 14-DEC-87

"INTERIM SUMMARY REPORT OF THE OPEN-LABEL PHASE
OF FOUR MULTICENTER, DOUBLE-BLIND PLACEBO-
CONTROLLED STUDIES TO DETERMINE THE EFFICACY AND
SAFETY OF ORALLY ADMINISTERED QUINAPRIL
HYDROCHLORIDE (CI-906) IN PATIENTS WITH ESSENTIAL
HYPERTENSION (PROTOCOLS 906-12, 906-13, 906-15
THROUGH 906-22, 906-30 THROUGH 906-38, 906-41
THROUGH 906-46, 906-82 THROUGH 906-86, 908-89
THROUGH 906-91, 906-93, 906-95, 906-96, 906-114
THROUGH 906-124, 906-126 THROUGH 906-131, 906-133
906-134, 906-137 AND 906-138)"

26-JAN-88 432 PR. 906-241-34 & X-34/INFORMATION AMENDMENT/PROTOCOL AMEND.
CONTENT:

REVISED PAGE RR 764-00131

PG. 11/12

DATE: 7-JAN-88

AMENDMENT NO. 3

PR. 906-123

DATE: 15-APR-87

ALLOWS FOR CONTINUATION OF OPEN-LABEL TREATMENT
FOR AN ADDITIONAL 12 MONTHS.

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26-JAN-88	433	INFORMATION AMENDMENT
CONTENT: REVISED PAGES X-720-02147 COMPLETE REPORT DATE: 8-DEC-87 CROSS REFERENCE: SERIAL #314		
26-JAN-88	434	INFORMATION AMENDMENT
CONTENT: RR 720-02332 AUTHOR: FRANK. G.J. ET AL DATE: 22-DEC-87 "OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 87, -89 TO 91, -93, -95, -96)"		
03-FEB-88	435	INFORMATION AMENDMENT
CONTENT: RR 4301-00025 AUTHOR: WOELFING, A. ET AL DATE: 11-SEP-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND PARALLEL 28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE A DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH TWICE A DAY ORALLY ADMINISTERED ENALAPRIL WHEN BOTH GIVEN IN ADDITION TO ONCE A DAY CHLORTHALIDONE IN PATIENTS WITH MODERATE TO SEVERE HYPERTENSION (CT 890-170)"		
03-FEB-88	436	PRS. 906-241-1 AND 906-241X-1/INFORMATION AMENDMENT
CONTENT: REVISED PAGES RR 720-02337 PGS. 22 AND 23 DATE: 18-JAN-88		
03-FEB-88	437	SAFETY REPORT
CONTENT: PATIENT NO.: 6 (SOP) PR. 906-68 AE: DEATH - CARDIAC ARREST NOT DRUG RELATED. FOLLOW-UP REPORT - SERIAL #348 AE 001-0906-870013-01		

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10-FEB-88 438 INFORMATION AMENDMENT

CONTENT:

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PGS. 21, 78, 79, 95, 266H/2261, 226J/267 AND 1932
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DATE: 18-JAN-88

10-FEB-88 439 INFORMATION AMENDMENT

CONTENT:

REVISED PAGES RR X-720-02327
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CROSS REFERENCE: SERIAL #387

24-FEB-88 440 INFORMATION AMENDMENT

CONTENT:

REVISED PAGE RR 720-02147
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DATE: 16-FEB-88

REVISED PAGE RR X-720-02185
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REVISED PAGE 720-02332
PGS. 2 AND 5
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PGS. 3, 4 AND 35
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24-FEB-88 441 INFORMATION AMENDMENT

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PGS. 2, 16, 965 THROUGH 980
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PG. 2
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REVISED PAGE RR 724-00081
PGS. 3, 5, 10 AND 22
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24-FEB-88	442	INFORMATION AMENDMENT
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REVISED PAGES RR 720-02337		
PGS. COVER SHEET, 2, 3, 4, 7, 8 14, 16, 21, 24-27,		
30, 33-36, 52 AND 54		
DATE: 22-FEB-88		
02-MAR-88		LETTER RE: REQUEST FOR INFORMATION
CONTENT:		
LETTER FROM: LIPICKY, RAYMOND J., M.D.		
RE: REQUEST FOR ADDITIONAL MANUFACTURING AND		
CONTROLS DATA.		
04-MAR-88	443	PR. 906-241-31/NEW SUB-INVESTIGATOR
CONTENT:		
PR. 906-241-32		
DUENSING, DAVID T., M.D.		
04-MAR-88	444	PR. 906-267-0
04-MAR-88	445	INFORMATION AMENDMENT
CONTENT:		
REVISED PAGES RR 762-00556		
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REVISED PAGES RR 720-02334		
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04-MAR-88	446	INFORMATION AMENDMENT
CONTENT:		
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PGS. 4, 18 AND 19		
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04-MAR-88 447 INFORMATION AMENDMENT
CONTENT:

REVISED PAGES RR X-720-02367
PGS. TITLE PAGE, 2, 5, 8, 14 AND 46
DATE: 26-FEB-88

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PGS. 3, 4, 8, 9, 10, 11 AND 20
DATE: 26-FEB-88

24-MAR-88 448 PR. 906-283-0

24-MAR-88 449 PROTOCOL AMENDMENT
CONTENT:

AMENDMENT NO. 3
PRS. 906-116, 117, 121, 122, 124, 126, 128, 129,
130 AND 131
DATE: 15-APR-87
ALLOWS FOR THE CONTINUATION OF OPEN-LABEL
TREATMENT FOR AN ADDITIONAL 12 MONTHS (TOTAL 24
MONTHS).

AMENDMENT NO. 4
PRS. 906-31, 34, 35, 36, 37, 42, 43, 45, 82, 83,
84, 85, 86, 89, 90, 91, 96 AND 124
DATE: 15-APR-87
ALLOWS FOR THE CONTINUATION OF OPEN-LABEL
TREATMENT FOR AN ADDITIONAL 12 MONTHS (TOTAL 24
MONTHS).

AMENDMENT NO. 5
PRS. 906-33 AND 44
DATE: 15-APR-87
ALLOWS FOR THE CONTINUATION... (TOTAL 24 MONTHS).

28-MAR-88 450 LETTER RE: MEETING REQUEST
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.
RE: PRE-NDA MEETING REQUEST:
1) DRAFT PACKAGE INSERT.
2) OVERVIEW OF THE CLINICAL PROGRAM.

12-APR-88 451 PRS. 906-241-29 & X-29, 35 & X-35

12-APR-88 452 PR. 906-258-2

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12-APR-88	453	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 3 PR. 906-226-2 DATE: 27-NOV-87 CHANGES THE EXERCISE TIME AND EXERCISE STAGES.		
12-APR-88	454	INFORMATION AMENDMENT
CONTENT: RR 764-00970 AUTHOR: HORVATH, A.M. ET AL DATE: 5-FEB-88 "CLINICAL DOSE-PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING SINGLE 2.5-MG. TO 80-MG. TABLET DOSES OF QUINAPRIL, PROTOCOL 906-259"		
22-APR-88	455	LETTER RE: CONFIRMING MEETING
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. RE: CONFIRMATION OF PRE-NDA MEETING ON 6-MAY-88 AT 10:00 A.M.		
09-MAY-88	456	INFORMATION AMENDMENT
CONTENT: REVISED PAGE RR 720-02349 COMPLETE REPORT DATE: 2-MAR-88		
09-MAY-88	457	PROTOCOL AMENDMENT/NEW SUB-INVESTIGATOR
CONTENT: AMENDMENT NO. 1 PR. 906-177 DATE: 2-APR-87 ADDS AN ASSESSMENT OF QUALITY OF LIFE AT THE LAST PLACEBO BASELINE VISIT AND AT THE END OF THE DOUBLE-BLIND. AMENDMENT NO. 4 PR. 906-226-1 DATE: NONE ALLOWS PATIENTS WHO HAVE PREVIOUSLY PARTICIPATED IN PR. 906-256-0 TO PARTICIPATE IN PR. 906-226-1. PR. 906-226-32 VAN DE NOBELEN, J.A.E.F.M.		

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09-MAY-88 CONTENT:	458	LETTER RE: CHEMISTRY, MANUFACTURING & CONTROLS LETTER TO: DIVISION OF CARDIO-RENAL RR X-929-00069 RE: UPDATES OUR MANUFACTURING AND CONTROLS DATA FOR THIS FORMULATION.
16-MAY-88 CONTENT:	459	PRS. 906-241-25 & X-25/PROTOCOL AMENDMENT AMENDMENT NO. 2 PR. 906-241-25
26-MAY-88	460	PR. 906-281-0
26-MAY-88 CONTENT:	461	INFORMATION AMENDMENT RR 764-01014 AUTHOR: OLSON, S.C. ET AL DATE: 8-APR-88 "MULTIPLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN RENAL FAILURE - PROTOCOL 906-AE"
27-MAY-88 CONTENT:	462	LETTER RE: MEETING REQUEST LETTER TO: LIPICKY, RAYMOND J., M.D. RE: REQUEST MEETING TO DISCUSS THE CHEMISTRY, MANUFACTURING AND CONTROL ISSUES.
27-MAY-88 CONTENT:	463	MINUTES OF FDA MEETING DATE: 9-MAY-88 PRE-NDA FDA MEETING
14-JUN-88 CONTENT:	464	LETTER RE: REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: WRITTEN REQUEST FOR COMMENTS ON SPECIFIC ITEMS CONCERNING THE NDA.
20-JUN-88 CONTENT:	465	INFORMATION AMENDMENT/PR. 906-227-21 RR 740-02456 AUTHOR: KRAUSE, B.R. ET AL DATE: 6-JUN-88 "EFFECT OF QUINAPRIL, CAPTORPIL, AND ENALAPRIL IN FRUCTOS-FED RATS" RR 740-02383 AUTHOR: RYAN, M.J. ET AL DATE: 7-JUN-88

FIVE-DAY DOSING STUDY IN RENAL HYPERTENSIVE RATS"

RR 740-02484

AUTHOR: RYAN, M.J. ET AL

DATE: 7-JUN-88

"ANTIHYPERTENSIVE ACTIVITY OF QUINAPIRL IN
HYDROCHLOROTHIAZIDE-TREATED CONSCIOUS
SPONTANEOUSLY HYPERTENSIVE RATS"

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20-JUN-88	465	INFORMATION AMENDMENT/PR. 906-227-21 - CONTINUED
CONTENT: RR 745-01248 AUTHOR: HURTT, M.E. ET AL DATE: 18-MAY-88 "RAT BONE MARROW CYTOGENETIC STUDY OF CI-906"		
01-JUL-88		LETTER RE: FDA REQUEST FOR INFORMATION
CONTENT: LETTER FROM: LIPICKY, RAYMOND J., M.D. RE: WRITTEN REQUEST FOR ADDITIONAL MANUFACTURING AND CONTROLS DATA.		
07-JUL-88	466	ANNUAL REPORT
CONTENT: CUTOFF DATE: 1-MAY-88		
07-JUL-88	467	PR. 906-273-0
19-JUL-88	468	LETTER RE: MINUTES OF FDA MEETING
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. RE: TELEPHONE CONVERSATION: 13-JUN-88 FOLLOW-UP ON THE PRE-NDA MEETING.		
26-JUL-88	469	PRS. 906-261 AND 906-282/PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 7 PR. 906-64 DATE: 1-JUN-88 ALLOWS THE EXTENSION OF THE OPEN-LABEL PHASE TO 36 MONTHS.		
04-AUG-88	470	PR. 906-293-0
10-AUG-88	471	MINUTES OF FDA MEETING
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. MINUTES OF 8-JUL-88 MEETING TO REVIEW CERTAIN CHEMISTRY, MANUFACTURING AND CONTROL ISSUES FOR THE SUBMISSION OF AN NDA.		
26-AUG-88	472	LETTER RE: PROTOCOL CANCELLATION/PROTOCOL AMD/INFOR. AMD.
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. PR. 906-273-0 RE: CANCELLATION OF PROTOCOL AMENDMENT NO. 1 PR. 906-273-0		

TO MODIFY THE LOWER LIMIT OF MEAN URINARY
ALBUMIN EXCRETION FROM 70MG PER DAY TO 50MG
PER DAY.

RR 740-02528

AUTHOR: KRAUSE, B.R. ET AL

DATE: 2-AUG-88

"EFFECT OF ACE INHIBITORS ON PLASMA LIPIDS IN
NORMAL RATS: CONFIRMATION OF TRIGLYCERIDE-
LOWERING EFFECT USING ORAL DOSING"

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26-AUG-88	473	INFORMATION AMENDMENT
CONTENT:		
RR 720-02386 AUTHOR: BERGHOFF, W. ET AL DATE: 18-AUG-88 "REPORT OF A COMPARISON OF QUINAPRIL (CI-906) AND CI-928 PLASMA CONCENTRATIONS WITH REDUCTION IN DIASTOLIC BLOOD PRESSURE DURING A 12-WEEK DOUBLE- BLIND STUDY IN PATIENTS WITH MODERATE TO SEVERE HYPERTENSION (PROTOCOL 906-82 THROUGH 906-87, 906-89 THROUGH 906-91, 906-92, 906-95, AND 906-96)"		
16-SEP-88	474	INFORMATION AMENDMENT/PROTOCOL AMENDMENT
CONTENT:		
RR 740-01519 AUTHOR: PACE, D.P. ET AL DATE: 30-AUG-88 "HEMODYNAMIC RESPONSES TO QUINAPRIL (CI-906) IN CONSCIOUS SODIUM-RESTRICTED FUROSEMIDE-TREATED DOGS"		
AMENDMENT NO. 8 PR. 906-64 CANCELLATION OF THE 3RD YEAR OF OPEN-LABEL.		
30-SEP-88	475	PROTOCOL AMENDMENT/NEW PRINCIPAL INVESTIGATOR/PR. 906-295
CONTENT:		
AMENDMENT NO. 8 PR. 906-68 DATE: NONE CANCELLATION OF THE 3RD YEAR OF OPEN-LABEL.		
PR. 906-131 HAUCH, THOMAS, M.D.		
30-SEP-88	476	INFORMATION AMENDMENT
CONTENT:		
RR 720-02388 AUTHOR: BECKER, M. ET AL DATE: 8-SEP-88 "REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-12, 906-13, AND 906-15 TO 906-22)"		

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14-OCT-88	477	INFORMATION AMENDMENT
CONTENT:		<p>RR 764-01083 AUTHOR: BERGER, P.J. ET AL DATE: 24-AUG-88 "A VALIDATED GAS CHROMATOGRAPHIC METHOD TO DETERMINE CI-906 AND ITS ACTIVE METABOLITE, CI-928, IN HUMAN URINE"</p> <p>RR 764-01094 AUTHOR: OLSON, S.C. ET AL DATE: 31-AUG-88 "COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN CLINICAL PHARMACOKINETIC STUDIES"</p>
14-OCT-88	477	INFORMATION AMENDMENT - CONTINUED
CONTENT:		<p>RR 764-01099 AUTHOR: OLSON, S.C. ET AL DATE: 31-AUG-88 "COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITES, QUINAPRILAT (CI-928), IN PRE-CLINICAL PHARMACOKINETIC STUDIES"</p>
14-OCT-88	478	INFORMATION AMENDMENT
CONTENT:		<p>RR 724-00093 AUTHOR: BECKER, M. ET AL DATE: 1-OCT-88 "REPORT OF A PLACEBO-CONTROLLED 24-HOUR BLOOD PRESSURE MONITORING STUDY OF ONCE AND TWICE DAILY ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOL 906-250-1 THROUGH 906-250-3)"</p>
14-OCT-88	479	PRS. 906-268-1 & 305-O/NEW SUB-INVESTIGATOR/PR. AMENDMENT
CONTENT:		<p>PR. 906-8 DENBLINDEN, J.L., M.D. GEORGE, B., M.D.</p> <p>AMENDMENT NO. 1 PR. 906-268 DATE: 15-SEP-88 THE FOLLOWING SECTIONS OF THE PROTOCOL HAVE BEEN CHANGED:</p> <ol style="list-style-type: none">1. A) SECTION IV G8, PAGE 16 B) TABLET 1, PAGE 21 C) APPENDIX 1, SECTION E, PAGE 252. PAGE 19, PARAGRAPH 3

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28-OCT-88	480	PR. 906-263-3/PROTOCOL AMENDMENT/NEW SUB-INVESTIGATOR
CONTENT:		<p>AMENDMENT NO. 1 PR. 906-263 DATE: 18-AUG-88 ALLOWS PATIENTS TO ENTER THE 24 WEEK OPEN-LABEL PHASE AFTER A TWO TO THREE WEEK PLACEBO BASELINE PERIOD.</p> <p>AMENDMENT NO. 2 PR. 906-263 DATE: 14-SEP-88 ALLOWS PATIENTS WITH A HEART RATE OF 55 OR GREATER BEATS PER MINUTE TO ENTER THE STUDY.</p> <p>PR. 906-238-5 GRIEGO, GENARA, M.D.</p>
28-OCT-88	481	INFORMATION AMENDMENT
CONTENT:		<p>RR 764-01061 AUTHOR: OLSON, S.C. ET AL DATE: 20-JUL-88 "A PRELIMINARY ESTIMATE OF THE EFFECTIVE ACCUMULATION HALF-LIFE FOR QUINAPRILAT"</p>
28-OCT-88	482	INFORMATION AMENDMENT
CONTENT:		<p>RR 764-01084 AUTHOR: HORVATH, A.M. ET AL DATE: 25-AUG-88 "THE PHARMACOKINETICS OF QUINAPRIL HCL AND ITS ACTIVE METABOLITE (QUINAPRILAT) IN PATIENTS WITH VARYING DEGREES OF RENAL FUNCTION - PROTOCOL 906-255"</p> <p>RR MEMO-764-01085 AUTHOR: HORVATH, A.M. ET AL DATE: 26-AUG-88 "THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE METABOLITE OF QUINAPRIL HCL, PD 109488, AND THE DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT, PD 113413, IN PATIENTS WITH VARYING DEGREES OF RENAL FUNCTION - PROTOCOL 906-255"</p>
03-NOV-88	483	PR. 906-263-1

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17-NOV-88	484	PR. 906-263-2
17-NOV-88	485	INFORMATION AMENDMENT
CONTENT: RR 764-01104 AUTHOR: KUGLER, A.R. ET AL DATE: 10-SEP-88 "DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM DIALYSIS METHOD TO DETERMINE QUINAPRIL AND QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"		
17-NOV-88	486	PR. 906-262 CENTERS 3, 7, 10, 11, 19 AND 20
01-DEC-88	487	PR. 906-262 CENTERS 16 & 18/NEW SUB-INVESTIGATOR
CONTENT: PRS. 906-241-1 AND 906-241-1X WEINRAUCH, VIKTOR WOLFGANG, M.D.		
14-DEC-88	488	INFORMATION AMENDMENTS
CONTENT: REVISED PAGES RR 720-02338 COMPLETE REPORT DATE: 30-SEP-88 CROSS REFERENCE: SERIAL #424		
14-DEC-88	489	INFORMATION AMENDMENT
CONTENT: RR X-720-02394 AUTHOR: BERMAN, S.J. ET AL DATE: 18-NOV-88 "AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOSE-RESPONSE MULTICENTER STUDY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-238-1 TO 5, 906-238-7 TO 16, AND 906-238-18 TO 26)"		
21-DEC-88	490	PR. 906-262 CENTERS 9, 17, 21/NEW SUB-INVESTIGATOR
CONTENT: PR. 906-261-11 BURTON, ALBERT, M.D., CHB, MRCGP		
21-DEC-88	490	LETTER RE: PROTOCOL CANCELLATION - CONTINUED
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. PR. 906-261-9 RE: CANCELLATION OF PROTOCOL.		

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21-DEC-88	491	PRS. 906-266-1 & 2
11-JAN-89	492	PR. 906-303-26
11-JAN-89	493	INFORMATION AMENDMENT
CONTENT: RR X-720-02392 AUTHOR: EVANS, R. ET AL DATE: 11-NOV-88 "INTERIM SUMMARY REPORT OF THE OPEN-LABEL PHASE OF FOUR MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDIES TO DETERMINE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH ESSENTIAL HYPERTENSION"		
30-JAN-89	494	PRS. 906-306-0, 307-0, 308-0, 314-0, 315-0
30-JAN-89	495	PR. 906-262-13/PROTOCOL AMENDMENTS/ADDENDUM
CONTENT: ADDENDUM NO. 1 PR. 906-109 ADDENDUM NO. 1 PR. 906-171 DATE: 2-APR-87 ADDENDUM NO. 1 PR. 906-252-1 AMENDMENT NO. 1 PR. 906-262-3 DATE: 3-JAN-89 AMENDMENT NO. 1 PR. 906-295 DATE: 7-DEC-88		
30-JAN-89	495	PROTOCOL AMENDMENTS/ADDENDUM - CONTINUED
CONTENT: AMENDMENT NO. 8 PR. 906-66		
30-JAN-89	496	INFORMATION AMENDMENT
CONTENT: RR 724-00085 AUTHOR: BERGHOFF, W. ET AL DATE: 8-DEC-88 "REPORT OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED TOLERANCE AND PHARMACOKINETIC STUDY OF SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN NORMAL SUBJECTS		

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08-FEB-89	497	PR. 906-303 CENTERS 1 THRU 17, 906-268-2, 906-277-0, 906-280
15-FEB-89	498	PR. 906-260 CENTERS 1 AND 2
CONTENT:		PR. 906-260-1 (JOSE A. YULDE, MD) 906-260-2 (MARCELITO DURANTE, MD)
08-MAR-89	499	PRS. 906-243-0, 279-0, 296-0, 262-22, 303-18, 303-24, 303-25
08-MAR-89	499	PROTOCOL AMENDMENT/LETTER RE: PR. CANCELLATION - CONTINUED
CONTENT:		AMENDMENT NO. 1 PR. 906-303 DATE: 21-DEC-88 STATES THAT CPK SHOULD BE INCLUDED IN ALL FULL LAB LABORATORY DETERMINATIONS (SCREENING, V1 AND V2), ALSO, DOUBLING THE MEDICATION DOSE AT THE END OF THE WEEK 4. PR. 906-132 RE: CANCELLATION OF PROTOCOL.
15-MAR-89	500	PR. 906-268-3, 303 CENTERS 20,21,22,23,28/PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-303 CORRECTION - AMENDMENT ONLY PERTAINS TO CENTERS NO. 1 THRU 19. CROSS REFERENCE: SERIAL #499
06-APR-89	501	PR. 906-319-0/NEW SUB-INVESTIGATOR
CONTENT:		PR. 906-262-19 PALUMBO, REMIGIO, M.D.
06-APR-89	502	PR. 906-303 CENTERS 27 AND 31
08-MAY-89	503	PRS. 906-268-4 & 906-328-0
08-MAY-89	504	INFORMATION AMENDMENT
CONTENT:		RR 764-01106 AUTHOR: KUGLER, A.R. ET AL DATE: 27-MAR-89 "IN VITRO QUINAPRIL METABOLISM IN RAT, DOG, MONKEY AND HUMAN LIVER PREPARATIONS"

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31-MAY-89	505	PRS. 906-333 CENTERS 1,10,11 AND 906-272-0/PR. AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-282 DATE: 24-AUG-88 CHANGES THE FOLLOWING: 1) SECTION IV CE, SUPINE BLOOD PRESSURE. 2) SECTION V E4, SUPINE HEART RATE. 3) SECTION VI B, BODY MASS INDEX > 30 KG/M2 OR <30 KG/M2. 4) APPENDIX 3, CLINICAL LABORATORY DETERMINATION AND ECG WILL BE PERFORMED AT SCREENING (Q.V. SECTION V A) AND AT THE END OF BASELINE.
07-JUN-89	506	ANNUAL REPORT
CONTENT:		CUTOFF DATE: 8-MAY-89
07-JUN-89	507	PR. 906-304-0
07-JUN-89	508	INFORMATION AMENDMENT
CONTENT:		RR 745-01350 AUTHOR: ULLOA, H.M. ET AL DATE: 9-MAY-89 "DERMAL SENSITIZATION STUDY OF CI-906 (QUINAPRIL) IN GUINEA PIGS (MAXIMINZATION TEST)" RR 745-01350 AUTHOR: DETHLOFF, L.A. ET AL DATE: 10-MAY-89 "THE EFFECTS OF CI-906 (QUINAPRIL) ON RENAL FUNCTION ON RENAL HEMODYNAMICS IN RATS" RR 745-01384 AUTHOR: MACDONALD, J.R. ET AL DATE: 9-MAY-89 "EFFECTS OF CI-906 ADMINISTERED ORALLY FOR FOUR WEEKS ON RENAL FUNCTIONAL PARAMETERS IN MALE RATS"
07-JUN-89	508	INFORMATION AMENDMENT - CONTINUED
CONTENT:		RR 745-01408 AUTHOR: HENCK, J.W. DATE: 12-MAY-89 "TWO-WEEK ORAL TOXICITY STUDY OF CI-906 IN FEMALE RABBITS" RR 745-01412 AUTHOR: PETRERE, J.A. ET AL DATE: 9-MAY-89 "MODIFIED PENINATAL-POSTNATAL STUDY IN RATS WITH CI-906"

RR 745-01421

AUTHOR: KROPKO, M.L.

DATE: 9-MAY-89

"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906
IN V79 CHINESE HAMSTER LUNG CELLS"

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07-JUN-89	508	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
RR 745-01430 AUTHOR: SUSICK, R.L. ET AL DATE: 9-MAY-89 "RENAL FUNCTION AND HEMODYNAMICS IN DOGS AFTER THIRTEEN-WEEK ORAL ADMINISTRATION OF CI-906"		
RR 745-01450 AUTHOR: GOUGH, A.W. ET AL DATE: 8-MAY-89 "HISTOPATHOLOGIC REVIEW OF KIDNEYS FROM RODENT CHRONIC TOXICITY STUDIES AND TUMOR BIOASSAYS WITH CI-906"		
14-JUN-89	509	PR. 906-333 CENTERS 2, 4 AND 5/NEW PRINCIPLE INVESTIGATOR
CONTENT:		
PR. 906-204-0 SAVRAN, STEPHEN, M.D.		
22-JUN-89		MEMO RE: DISCUSSION WITH FDA
CONTENT:		
RE: DISCUSSION ON 15-JUN-89 AFTER MEETING: 1) NDAS ON ACE INHIBITORS WOULD NOT BE BROUGHT BEFORE THE ADVISORY COMMITTEE 2) DEVELOPMENT ON ACE INHIBITORS/CALSIUM CHANNEL BLOCKER COMBINATION COULD BE APPROVED, BUT DEVELOPMENT MAY BE TECHNICALLY DIFFICULT.		
22-JUN-89	510	PR. 906-309-0
29-JUN-89	511	PRS. 906-333 CENTERS 3, 6, 7 AND 906-33X CENTERS 3 AND 7
13-JUL-89	512	PRS. 906-330-0, 906-333 AND 333X CENTERS 9 & 12
27-JUL-89	513	PRS. 906-331-0/327-2,7,9,10/333 & 333X-2,9,10/263-4/273-1,2
27-JUL-89	514	INFORMATION AMENDMENT
CONTENT:		
RR 740-02642 AUTHOR: TAYLOR, D.G. DATE: 23-JUN-89 "THE EFFECTS OF QUINAPIRL (Q) ON SYSTEMIC AND REGIONAL HEMODYNAMICS AND CARDIAC MASS IN WISTAR- KYOTO (WKY) AND SPONTANEOUSLY HYPERTENSIVE (SHR) RATS"		

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03-AUG-89 CONTENT:	515	NEW SUB-INVESTIGATOR PR. 906-262-22 CAVERO, PATRICIA, M.D.
03-AUG-89	515	PRS. 906-327 & 327X CENTERS 5 AND 6
17-AUG-89	516	PRS. 906-327 & 327X CENTERS 1 AND 11/PR. 906-327-4
24-AUG-89	517	PR. 906-303-30
14-SEP-89	518	PRS. 906-335-0, 906-336-0, 906-327 & 327X-8
14-SEP-89 CONTENT:	518	NEW SUB-INVESTIGATOR/PROTOCOL AMENDMENT PR. 906-333-6 DRUEGER, DAVID, M.D. NAWAZ, DILSHER, M.D. AMENDMENT NO. 1 PR. 906-304-0 THE DOSE OF DIURETIC MAY BE ADJUSTED IN RESPONSE TO PATIENT SYMPTOMS. HOWEVER, THE DOSE OF DIURETIC MUST BE STABILIZED AND CONSISTENT.
14-SEP-89 CONTENT:	519	INFORMATION AMENDMENT RR 4301-00047 AUTHORS: BABOVIC-ALT, R. WIDMER, W. DATE: 4-AUG-89 "RANDOMIZED, SINGLE-BLIND CROSSOVER STUDY COMPARING THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH DIGOXIN ADDED TO HYDROCHLOROTHIAZIDE THERAPY IN PATIENTS WITH CONGESTIVE HEART FAILURE NYHA II (CT 891-002)" RR 4301-00051 AUTHORS: BALKOVIC-ALT, R. LILIENTHAL, J. DATE: 4-AUG-89 "REPORT OF A ONE-YEAR, OPEN-LABEL, MULTICENTER STUDY FOLLOWING A 12-WEEK, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED CI-906 (QUINAPRIL (CT 891-140)"

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14-SEP-89 519 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR 740-02586

AUTHORS: CASAD, B.
KEISER, J.

DATE: 28-AUG-89

"A MULTIPLE-DOSE STUDY TO ASSESS THE FUNCTIONAL
INTERACTION OF QUINAPRIL (CI-906) AND
HYDROCHLOROTHIAZIDE (CI-570) IN SALINE-LOADED
NORMOTENSIVE RATS"

28-SEP-89 520 PRS. 906-327 & 327X CENTER 3

28-SEP-89 521 INFORMATION AMENDMENT
CONTENT:

RR 740-02536

AUTHOR: RAPUNDALO, S. ET AL

DATE: 31-AUG-89

"COMPARATIVE EFFECTS OF QUINAPRIL AND QUINAPRILAT
ON VARIOUS PROTEINASES"

RR 740-02694

AUTHOR: CASAD, B. ET AL

DATE: 1-SEP-89

"A MULTIPLE-DOSE STUDY TO ASSESS THE FUNCTIONAL
INTERACTION OF QUINAPRIL (CI-906) AND
HYDROCHLOROTHIAZIDE (CI-570) IN SALINE-LOADED
SPONTANEOUSLY HYPERTENSIVE RATS"

12-OCT-89 522 PR. 906-321-0

26-OCT-89 523 PR. 906-334 CENTERS 1, 2, 3, 4, 5 AND 6
CONTENT:
The coinvestigators shall conduct this protocol at
their respective centers.

31-OCT-89 524 LETTER RE: CONFIRMATION OF MEETING
CONTENT:
LETTER TO: LIPICKY, RAYMOND J., M.D.
RE: CONFIRMATION OF PRE-NDA MEETING ON 28-NOV-89
AT 10 AM.
ATTACHED DRAFT REPORT (RR 720-02593) FOR
PR. 906-241.

14-NOV-89 MEMO RE: VERBAL CONFIRMATION
CONTENT:
TELEPHONE CONVERSATION WITH KATHLEEN BONGIOVANNI.
re: Confirmation that Dr. Temple would be at the
18-NOV-89 PRE-NDA MEETING.

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14-NOV-89 CONTENT:	525	PRS. 906-215, 317 & 341-0/NEW SUB-INVESTIGATOR PR. 906-224 NORTHRIDGE, DAVID, MRCP
14-NOV-89 CONTENT:	525	PROTOCOL ADDENDUMS/AMENDMENT ADDENDUM NO. 1 PR. 906-215 ADDENDUM NO. 2 PR. 906-224 AMENDMENT NO. 3 PR. 906-224 DATE: 7-DEC-88
01-DEC-89 CONTENT:	526	SAFETY REPORT PATIENT NO.: 8 (LL) PR. 906-331-0 AE: SUSPECTED HEPATITIS. DEATH WAS CONTRIBUTED TO PEPTIC ULCER DISEASE. WAS SUBMITTED AS A "CLINICAL INFORMATION AMENDMENT." AE 001-0906-890035-00
08-DEC-89 CONTENT:	527	MINUTES OF FDA MEETING 28-NOV-89 FDA PRE-NDA MEETING ON CI-955.
11-DEC-89 CONTENT:		MEMO RE: VERBAL REQUEST FOR INFORMATION TELEPHONE CONVERSATION WITH KATHLEEN BONGIOVANNI, FDA. RE: CLINICAL REPORT SENT 1-DEC-89 (REPORT OF HEPATITIS): 1) REQUESTED RESULTS OF MICROSCOPIC EXAMINATION. 2) QUESTIONED WHY SUBMISSION WAS SENT UNDER "CLINICAL INFORMATION".
13-DEC-89 CONTENT:		MEMO RE: VERBAL REQUEST FOR INFORMATION TELEPHONE CONVERSATION FROM DR. CHERYL GRAHAM, FDA RE: CLINICAL REPORT SENT 1-DEC-89 (REPORT OF HEPATITIS). ASSESSMENT SHOULD BE SENT TO ALL INVESTIGATORS.

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20-DEC-89 MEMO RE: VERBAL REQUEST FOR INFORMATION
CONTENT: TELEPHONE CONVERSATION STATING DR. B. FREIDMAN
IS NOW OUR QUINAPRIL IND MEDICAL REVIEWER.

20-DEC-89 528 LETTER RE: SUBMISSION CORRECTION
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D.
RE: SERIAL #526 CATEGORY.
RECATEGORYIZE 1-DEC-89 LETTER FROM "CLINICAL
INFORMATION AMENDMENT" TO "IND SAFETY REPORT".

20-DEC-89 529 PR. 906-311 CENTERS 1, 3, 5, 6 AND 8

02-JAN-90 MEMO RE: VERBAL REQUEST FOR INFORMATION
CONTENT: TELEPHONE CONVERSATION WITH DR. FRIEDMAN.
RE: QUINAPRIL IND AND NDA.
1) DR. JOHN VILLUAME HAS LEFT PARKE-DAVIS.
2) CONFIRMING HIS APPOINTMENT AS MEDICAL REVIEWER.
3) REVIEW OF THE PRE-NDA MEETING FOR CI-955.

03-JAN-90 530 SAFETY REPORT
CONTENT: PATIENT NO.: 8 (LL)
PR. 906-331-0
AE: SUSPECTED HEPATITIS.
POSSIBLE DRUG RELATED.
FOLLOW-UP REPORT - SERIAL #526
AE 001-0906-890035-00

05-JAN-90 MEMO RE: VERBAL REQUEST FOR INFORMATION
CONTENT: TELEPHONE CALL FROM KATHLEEN BONGIOVANNI, FDA.
RE: 10-DAY SAFETY REPORT FOLLOW-UP (SERIAL #526).
DR. FRIEDMAN RECEIVED FAX, PLACE HOLD ON
INVESTIGATOR'S LETTER UNTIL FDA REVIEW IS
COMPLETED.

11-JAN-90 531 PR. 906-312 CENTERS 0,2,4,5,6,7,14 & 15/NEW PRIMARY INVEST.
CONTENT: PR. 906-262-11
O'ROURKE, ROBERT, M.D.

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17-JAN-90	532	SAFETY REPORT
CONTENT:		PATIENT NO.: 8 (LL) PR. 906-331-0 AE: SUSPECTED HEPATITIS. POSSIBLE DRUG RELATED. FOLLOW-UP REPORT - SERIAL #526 REVISED INVESTIGATOR'S LETTER. AE 001-0906-890035-00
01-FEB-90	533	PROTOCOL AMENDMENT
CONTENT:		AMENDMENT NO. 1 PR. 906-340 PROVIDES FOR ADDITIONAL REQUIREMENTS SPECIFIED BY THE TWO GERMAN IRBS FOR PATIENT SCREENING AND PLACEBO BASELINE.
01-FEB-90	534	INFORMATION AMENDMENT
CONTENT:		RR 720-02398 AUTHOR: CANTER, D.A. ET AL DATE: 11-OCT-89 "A 12-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOLS 906-63 TO -69, -72 TO -75, -77 TO -79, -204, -205, -216, -218, -219, -233-2, AND -233-5)" RR 720-025821)" AUTHOR: CANTER, D.A. ET AL DATE: 22-DEC-89 "A 14-WEEK, OPTIONAL-TITRATION, MULTICENTER, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN PATIENTS WITH MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL 906-100, -102 TO -106, -109 TO -111)"
01-FEB-90	534	INFORMATION AMENDMENT - CONTINUED
CONTENT:		RR 764-01367 AUTHOR: BMMERT, J.A. ET AL DATE: 30-NOV-89 "A BIOAVAILABILITY STUDY OF QUINAPRIL HCL 20-MG COMMERCIAL TABLETS, 20-MG INVESTIGATIONAL CAPSULES, AND A 20-MG ORAL SOLUTION IN HEALTHY VOLUNTEERS: PROTOCOL 906-328"

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08-FEB-90	535	LETTER RE: REQUEST FOR REVIEW AND COMMENTS
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. RE: PR. 906-276		
08-FEB-90	536	PR. 906-313-0
15-FEB-90	537	LETTER TO: PROTOCOL CANCELLATION
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. PR 906-262-18 RE: CANCELLATION OF PROTOCOL		
15-FEB-90	537	PRS. 906-343 & 343X-0, PR. 906-311 CENTERS 4, 7, 10 & 11
22-FEB-90	538	INFORMATION AMENDMENT/IB UPDATE
CONTENT: RR 764-01432 AUTHOR: OLSON, S.C. ET AL DATE: 22-JAN-90 "EFFECTIVE ACCUMULATION HALF-LIFE FOR QUINAPRILAT FOLLOWING QUINAPRIL DOSING: PROTOCOL 906-305-0" DATE: 9-MAY-89 RR X-720-02572 AUTHORS: DAWKIN, R. PURCELL, T.J. SUPERSEDES RR X-720-02277		
01-MAR-90	539	PR. 906-340 CENTERS 5 AND 7/PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-340-7 DATE: 8-SEP-89 PROVIDES FOR ADDITIONAL REQUIREMENTS SPECIFIED BY THE IRB.		
01-MAR-90	540	PR. 906-340 CENTERS 21 & 22, PR. 906-346-0
05-MAR-90		MEMO RE: VERBAL REQUEST FOR INFORMATION
CONTENT: TELEPHONE CONVERSATION OF 2-MAY-90 & 5-MAY-90. RE: PROPOSED CHF STUDY 906-276. 1) INCONSISTENCE IS IN INFORMATION ON PAGES 5, 11 AND 19. (2-MAY-90) 2) REQUESTED INPUT ON THE USE OF EXERCISE TOLERANCE. (2-MAY-90) 3) REQUESTED SAMPLE CASE REPORT FORM. (5-MAY-90) 4) EXERCISE TOLERANCE IS A SUITABLE PRIMARY EFFICACY PARAMETER. (5-MAY-90) 5) WANT TO REVIEW GUIDELINES ON CHF. (5-MAY-90)		

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14-MAR-90 CONTENT:	541	LETTER RE: REQUEST FOR REVIEW AND COMMENTS LETTER TO: LIPICKY, RAYMOND J., M.D. RE: PROTOCOL 906-239. CROSSFILE IND 34,487 (CI-955)
22-MAR-90 CONTENT:	542	PRS. 906-344-0 & 902-348-0/NEW SUB-INVESTIGATOR PR. 906-268-4 GUEZI, BOUALEM, M.D.
29-MAR-90	543	PR. 906-340 CENTERS 14, 25, 26 AND 28
19-APR-90	544	PRS. 906-311-2 & 12/906-312-12/906-340 CNTS 1,2,16,17,23,24
26-APR-90	545	PRS. 906-276-1,2,3,6,9,12,14,22/310-13,30,39,42,43,44/345-13
01-MAY-90 CONTENT:		MEMO RE: REQUEST FDA MEETING MEMO RE: TELEPHONE CONVERSATION ON 23-APR-90 REGARDING A FDA VISIT.
03-MAY-90	546	PRS. 906-376 CENTERS 8, 16/906-355 CENTERS 1 THRU 10
10-MAY-90 CONTENT:		LETTER FROM FDA RE: MINUTES OF FDA MEETING LETTER FROM: MORGENSTER, NATALIA A. DATE: 28-NOV-89 FDA MINUTES
14-MAY-90	547	PRS. 906-345 CENTERS 31-34, 37,38/906-276 CENTERS 3,7,13
15-MAY-90 CONTENT:		MINUTES OF FDA MEETING DATE: 28-NOV-89 FDA MEETING RE: PRE-NDA MEETING FOR QUINAPRIL/HCTZ COMBINATION PRODUCT
18-MAY-90 CONTENT:	548	LETTER RE: INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: GENERAL CORRESPONDENCE

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21-MAY-90	549	PRS. 906-276 CENTERS 5,11,25/906-340 CENTERS 10,11,12,13,27
21-MAY-90	549	PR. 906-345 CENTERS 14,35,36,40,41,45,46,47 AND 48
30-MAY-90	550	PR. 906-276-10
06-JUN-90	551	PR. 906-276-20
18-JUN-90 CONTENT:	552	NEW PRINCIPLE INVESTIGATOR/AMENDMENT PR 906-276/906-276X-15 COLFER, HARRY, M.D. PR 906-276/906-276X-19 BAIRD, MICHAEL G., M.D. AMENDMENT NO. 1 PR 906-276 AND 906-276X DATE: 25-MAY-90 CHANGES ON PAGES 8, 10, 12, 13, 16 AND 19 DATE: 15-MAY-90 CHANGES ON PAGES 2 AND 3
18-JUN-90 CONTENT:	553	INFORMATION AMENDMENT RR 4301-00064 AUTHORS: SCHLUTTENHOFER, H ET AL DATE: 28-FEB-90 "A SINGLE-BLIND STUDY TO EVALUATE TOLERANCE AND EFFICACY OF A WEEK OF CONCOMITANT THERAPY WITH DILTIAZEM AND QUINAPRIL FOLLOWING A WEEK OF MONOTHERAPY WITH QUINAPRIL IN PATIENTS WITH HYPERTENSION (PROTOCOL 906-252)" RR 720-02735 AUTHORS: CANTER, D ET AL DATE: 01-MAR-90 "AN 18-WEEK, DOUBLE-BLIND, OPTIONAL-TITRATION, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL AND PLACEBO IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE (PROTOCOLS 906-226-01 TO -16, -18 TO -30, 32 TO -34)"

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18-JUN-90	553	INFORMATION AMENDMENT - CONTINUED
CONTENT:		<p>RR 720-02703 AUTHORS: CANTER, D ET AL DATE: 05-MAR-90 "A 12-WEEK, DOUBLE-BLIND CROSSOVER STUDY EVALUATING THE ANTIHYPERTENSIVE EFFECTS OF ONCE AND TWICE DOSE DAILY QUINAPRIL HYDROCHLORIDE (CI-906) ON 24-HOUR AMBULATORY BLOOD PRESSURE AND LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ESSENTIAL HYPERTENSION (PROTOCOL 906-289-0, 9-011-0)"</p>
18-JUN-90	553	INFORMATION AMENDMENT - CONTINUED
CONTENT:		<p>RR 720-02705 AUTHORS: CANTER, D ET AL DATE: 26-APR-90 "SAFETY REPORT OF AN EIGHT-WEEK, SINGLE-CENTER, DOUBLE-BLIND STUDY OF THE EFFECTS OF FOUR DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) ON THE RENIN-ANGIOTENSIN-ALDOSTERONE-CATECHOLAMINE AXIS IN PATIENTS WITH HYPERTENSION (PROTOCOL 906-213-0, 9-015-0)"</p>
18-JUN-90	554	INFORMATION AMENDMENT
CONTENT:		<p>RR 760-00011 AUTHOR: SCHRIER, D DATE: 16-FEB-90 "THE EFFECTS OF QUINAPRIL, CAPTOPRIL, AND ENALAPRIL IN CARRAGEENAN FOOTPAD EDEMA (CFE), A RAT ACUTE MODEL OF INFLAMMATION"</p> <p>RR 740-02796 AUTHORS: RYAN, MJ ET AL DATE: 26-FEB-90 "ANTI-HYPERTENSIVE ACTIVITY OF QUINAPRIL GIVEN FOR 14 DAYS TO CONSCIOUS SPONTANEOUSLY HYPERTENSIVE RATS"</p>
18-JUN-90	554	INFORMATION AMENDMENT - CONTINUED
CONTENT:		<p>RR 740-02799 AUTHORS: HALEEN, SJ ET AL DATE: 05-MAR-90 "THE EFFECTS OF QUINAPRIL ON THE TEMPORAL PROGRESSION OF LEFT VENTRICULAR FAILURE IN THE CARDIOMYOPATHIC HAMSTER"</p> <p>RR 4192-00422 AUTHORS: NEUB, M ET AL DATE: 23-APR-90 "DOSE-PROPORTIONALITY AND SYSTEMIC EXPOSURE OF QUINAPRILAT IN MICE AND RATS FOLLOWING MULTIPLE DOSE REGIMENS OF QUINAPRIL (PRECLINICAL PROTOCOLS</p>

90-001 AND 90-002)"

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DOC DATE	SER/SUPPL NO	TITLE
25-JUN-90 CONTENT:	555	NEW PRINCIPAL INVESTIGATORS 906-276-17 WALTERS, DAVID, M.D. 906-276-23 PANTAZOPOULOS, J, M.D. 906-276-24 SINGH, STEVEN, M.D. 906-345-01 LEARY, WP, PROF. 906-345-02 MYBURGH, DP, M.D. 906-345-03 SARELI, P, M.D.
25-JUN-90 CONTENT:	555	NEW PRINCIPAL INVESTIGATORS - CONTINUED 906-345-11 HENDRIKA, J, M.D. 906-345-17 BUONINCONTI, RAFFAELLO, PROF.
11-JUL-90 CONTENT:		FDA CONTACT MEMO MEMO RE: CI-906 CONTACT PERSON: FRIEDMAN, DR. TELEPHONE CONVERSATION RE: REQUEST FOR CLARIFICATION OF CAUSES OF DEATH IN STUDY 906-226.
12-JUL-90 CONTENT:		FDA CONTACT MEMO MEMO RE: CI-906 FDA CONTACT PERSON: FRIEDMAN, BASIL, DR. TELEPHONE CONVERSATION RE: FOLLOW-UP TO REQUEST FOR CLARIFICATION OF COURSES OF DEATH - STUDY 906-226.
12-JUL-90 CONTENT:	556	PROTOCOL AMENDMENT - NEW PRINCIPLE / SUB INVESTIGATORS AMENDMENT NO. 1 PR. 906-345-11 DATE: 12-JUL-90 AMENDMENT PERTAINS TO THIS SITE ONLY; PURPOSE IS TO SATISFY THE ETHICAL COMMITTEE REQUIREMENT THAT IF A PATIENT'S DIASTOLIC BLOOD PRESSURE RISES TO 100 NNHG OR MORE DURING PLACEBO THE PATIENT WILL WITHDRAW.

PR. 906-345-12
HOUTZAGERS, J.J.R., M.D.

PR. 906-345-18
WESTER, ANNO

PR. 906-340-15
ROSENQVIST, ULF

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DOC DATE	SER/SUPPL NO	TITLE
12-JUL-90 CONTENT:	556	AMENDMENT - NEW PRINCIPLE / SUB INVESTIGATORS - CONTINUED PR. 906-340-19 TASKINEN, ESKO SUBINVESTIGATOR'S PR. 906-311-10 MCDAID, P. DR. PR. 906-282 STARK, SANDRA
12-JUL-90 CONTENT:	557	INFORMATION AMENDMENT RR 740-02797 AUTHORS: PANEK, R.L. ET AL DATE: 13-JUN-90 "ANTIHYPERTENSIVE RESPONSE TO QUINAPRIL: ROLE OF CIRCULATING AND TISSUE ANGIOTENSIN CONVERTING ENZYME (ACE) ACTIVITY"
12-JUL-90 CONTENT:	558	INFORMATION AMENDMENT RR 4301-00055 AUTHORS: SCHLUTTENHOFER, H, ET AL DATE: 30-MAY-90 "A SINGLE-BLIND PILOT TO EVALUATE TOLERANCE AND EFFICACY OF A WEEK OF CONCOMITANT THERAPY WITH QUINAPRIL AND DILTIAZEM FOLLOWING A WEEK OF MONOTHERAPY WITH DILTIAZEM IN INPATIENTS WITH HYPERTENSION (PROTOCOL 906-251)" RR 764-01432 AUTHORS: OLSON, S.C. ET AL DATE: 22-JAN-90 "EFFECTIVE ACCUMULATION HALF-LIFE FOR QUINAPRILAT FOLLOWING QUINAPRIL DOSING: PROTOCOL 906-305-0"
12-JUL-90 CONTENT:	558	INFORMATION AMENDMENT - CONTINUED RR 764-01473 AUTHORS: BMMERT, J.A. ET AL DATE: 11-APR-90 "ABSOLUTE BIOAVAILABILITY AND PHARMACOKINETICS OF QUINAPRILAT IN HEALTHY VOLUNTEERS FOLLOWING SINGLE-DOSE ADMINISTRATION OF ORAL QUINAPRIL (CI-906) AND INTRAVENOUS QUINAPRILAT (CI-928): PROTOCOL 906-342"

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13-JUL-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CI-906/CI-955
CONTACT PERSON: WOLTERS, ROBERT, DR.
MEETING RE:
QUESTION ON PENDING QUINAPRIL NDA FUTURE Q/HCTZ
NDA EA

19-JUL-90 559 PROTOCOL AMENDMENT - NEW PRINCIPLE INVESTIGATOR
CONTENT:

AMENDMENT NO. ONE
PR. 906-349
THE ADDITION OF AN AUTOMATED BLOOD PRESSURE
MONITOR RECORDING AT WEEK 12 OF THE DOUBLE-BLIND
PERIOD.

PR. 906-349-07
BARRY, PAULL, M.D.

PR. 906-349-11
WOMBOLT, DUANE, G., M.D.

PR. 906-276-13
BAILEY, JOHN, M.D.

19-JUL-90 560 ANNUAL REPORT
CONTENT:

ISSUE DATE: 16-JUL-90

19-JUL-90 561 LETTER RE: REPLY TO FDA QUESTIONS OF 11-JUL-90
CONTENT:

LETTER TO: LIPICKY, RAYMOND, J., M.D.
TELEPHONE CONVERSATION:
REQUEST FOR ADDITIONAL INFORMATION ON PATIENTS
WHO DIED DURING STUDY PROTOCOL 906-226

26-JUL-90 562 PROTOCOL AMENDMENTS - NEW INVESTIGATOR
CONTENT:

AMENDMENT NO. 1
PR. 906-340-15
TO ALLOW PROLONGED TREATMENT OF PATIENTS HAVING
BENEFITFROM THE 906-340 STUDY.

AMENDMENT NO. 1
PR. 906-340-22
INTENSIFY BLOOD PRESSURE FOR PATIENTS WITH SEVERE
HYPERTENSION DURING THE BASLINE PLACEBO PHASE AND
TAKE THE LEVEL OF SYSTOLIC BLOOD PRESSURE INTO
CONSIDERATION.

PR. 906-340-08
PUJADES, JUAN, OCON, M.D.

PR. 906-340-09
CONZALEZ, RAMON, DOMERO, M.D.

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DOC DATE	SER/SUPPL NO	TITLE
26-JUL-90	562	PROTOCOL AMENDMENT - NEW INVESTIGATOR - CONTINUED
CONTENT:		PR. 906-349-1 WEINER, GERALD, M., M.D. PR. 906-349-5 MARBURY, THOMAS, C., M.D. PR. 906-349-8 ROSENBAUM, ROBERT, M.D.
26-JUL-90	563	INFORMATION AMENDMENT
CONTENT:		RR 4301-00060 AUTHORS: EYSELL, J., ET AL DATE: 18-APR-90 "REPORT ON A TWELVE-WEEK, DOUBLE-BLIND, PARALLEL- GROUP, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF CI-906 (QUINAPRIL HYDROCHLORIDE) AND CAPTOPRIL, WHEN ORALLY ADMINISTERED IN ADDITION TO HYDROCHLOROTHIAZIDE TO PATIENTS WITH MODERATE TO SEVERE ESSENTIAL HYPERTENSION (WLI 9-030-0)"
27-JUL-90	564	SAFETY REPORT
CONTENT:		PATIENT NO.: NONE (VAT) FRANCE AE: ANAPHYLACTIC SHOCK AE 033-0906-900058-00
02-AUG-90	565	INFORMATION AMENDMENT
CONTENT:		RR MEMO 720-02809 AUTHORS: CANTER, D. ET AL DATE: 17-JUL-90 "AN INTERIM REPORT ON THE EFFICACY AND SAFETY OF QUINAPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION AND MODERATE TO SEVERE CONCOMITANT RENAL IMPAIRMENT (PROTOCOLS 906-263-1 THROUGH 906-263-4 AND 906-268-1, 906-268-2 AND 906-268-4)"
02-AUG-90	566	NEW INVESTIGATOR / PROTOCOL AMENDMENT
CONTENT:		PR 906-349-2 GOLDSTEIN, MARK, M.D. PR 906-345-10 IKRAM, HAMID, M.D. NEW SUBINVESTIGATORS PR 906-311 WILLIAMS, PETER, HOWARD, M.D. MAXWELL, STEVEN, RICHARD, M.D.

SPECIAL AMENDMENT
PR. 906-349-2 (ONLY)
DATE: 15-JUN-90
PURPOSE IS TO DECREASE THE UPPER LIMIT OF THE
ENTRY CRITERIA FOR DIASTOLIC BLOOD PRESSURE TO
110 MM HG

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09-AUG-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CI-906
CONTACT PERSON: FRIEDMAN, BASIL, DR.
TELEPHONE CONVERSATION:
CLARIFICATION OF INFORMATION IN RR 4301-00060

09-AUG-90 567 NEW PRINCIPLE INVESTIGATOR
CONTENT:

PR. 906-345-21
QUOIDBACH, ALBERT, M.D.

PR. 906-345-24
LAVILLE, MAURICE, M.D.

PR. 906-349-06
NEDELMAN, PHILIP, M.D.

PR. 906-349-09
SILBAUGH, BARRY, M.D.

13-AUG-90 568 RESPONSE TO FDA REQUEST FOR INFORMATION
CONTENT:

LETTER TO: LIPICKY, RAYMOND, J., M.D.
CI-906
RE: RESPONSE TO TELEPHONE CONVERSATION FROM
FRIEDMAN, BASIL, DR. ON 09-AUG-90; TWO
QUESTIONS CONCERNING STUDY REPORT ON PROTOCOL
9-030-0.

16-AUG-90 569 NEW PRINCIPLE INVESTIGATOR
CONTENT:

PR. 906-349-03
HORWITZ, LAWRENCE, M.D.

PR-906-349-04
IDSV00G, PETER, M.D.

PR. 906-349-12
YELLEN, LAURENCE, G., M.D.

PR-906-276-21
REDDY, C.V., M.D.

21-AUG-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CI-906
FDA CONTACT PERSON: BONGIOVANNI, K.
MEETING AT FDA RE:
STATUS OF PENDING QUINAPRIL NDA.

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DOC DATE	SER/SUPPL NO	TITLE
23-AUG-90	570	PROTOCOL AMENDMENT / NEW PRINCIPLE INVESTIGATOR
CONTENT:		AMENDMENT NO. 1 PR.906-345 EXCLUDES PATIENTS WITH BRADYCARDIA (HEART RATE < 5 5); ALLOWS INCLUSION OF PATIENTS WITH HEART RATE > 50. THIS CHANGE WAS REQUESTED BY THE ETHICAL COMMITTEE IN FINLAND.
30-AUG-90	571	PR. 423-906-350/NEW SUB-INVESTIGATORS
CONTENT:		PR. 906-282 STARK, SISTER SANDRA PR. 906-311-10 MCCAID, P., M.D.
30-AUG-90	572	LETTER RE: FOLLOW UP TO SAFETY REPORT
CONTENT:		LETTER TO: LIPICKY, RAYMOND, J., M.D. RE: FOLLOW UP TO A WRITTEN SAFETY REPORT (SERIAL NO. 564, JULY 27, 1990).
06-SEP-90	573	INFORMATION AMENDMENT
CONTENT:		RR 720-02817 AUTHORS: KIMMEL, K.A., ET AL DATE: 23-AUG-90 "INITIAL REPORT OF THE PRIMARY EFFICACY ANALYSIS OF A 24-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-TITRATION, MULTICENTER, THREE-WAY CROSSOVER STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) QD AND BID IN THE TREATMENT OF PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOLS 906-215, -224, AND -295)"
06-SEP-90	574	NEW PRINCIPLE INVESTIGATOR
CONTENT:		PR 906-345-19 MIEVIS, ERIC, M.D. PR 906-349-10 WHELTON, ANDREW, M.D.
13-SEP-90	575	NEW PRINCIPLE INVESTIGATOR / PROTOCOL AMENDMENT
CONTENT:		PR. 906-276-27 ZELLNER, STEPHEN, R., M.D. PR. 906-317 SAAL, JEAN-PIERRE, M.D. WILL WORK UNDER CASTAIGNE, ALAIN, M.D.

PR. 906-346-0

DATE: 26-FEB-90

THIS AMENDMENT ASSURES THAT THE NEWEST PUERTO RICO
FORMULATIONS ARE USED IN THIS STUDY.

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18-SEP-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CI-906
FDA CONTACT PERSON: BONGIOVANNI, K.
TELEPHONE CONVERSATION RE:
QUESTION ON RR 4301-00060 IN SERIAL NO. 563

SURVEY ON PEDIATRICS STUDIES FOR NDA PRODUCTS
IS UNDER REVIEW; SHE IS FAXING A COPY OF THE
SURVEY AND WOULD LIKE US TO RESPOND IN A LETTER
TO OUR NDA.

27-SEP-90 576 NEW PROTOCOL / NEW SUB-INVESTIGATOR'S
CONTENT:

PR. 906-352 CENTERS 1 AND 2
INTERNATIONAL STUDY NUMBER
421-906-014 CENTERS 1 AND 2

PR. 906-350-0
INTERNATIONAL STUDY NUMBER
906-350-410

NEW SUB-INVESTIGATOR'S
906-276-22
ABELL, MARY, M.D.
FARUQ, DALIRA, M.D.

11-OCT-90 577 PR. 906-357 CENTERS 1,2,3,4,5,6,7,/906-276-29/NEW SUB-INVEST
CONTENT:
PR. 906-276-3
CARBERRY, PETER A., M.D.

22-OCT-90 578 PR. 906-276-28/NEW PRINCIPLE INVESTIGATOR
CONTENT:
PR. 906-311-9
AMIN, M.S., DR.

31-OCT-90 579 PR. 906-351-0 (906-001-455)/PROTOCOL AMENDMENT
CONTENT:
AMENDMENT NO. 1
PR. 906-351-0
CLARIFIES THE INCLUSION AND EXCLUSION CRITERIA.

08-NOV-90 580 PR. 906-345X-3

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DOC DATE	SER/SUPPL NO	TITLE
16-NOV-90	581	PR. 906-345-20/PR. 906-325-0
26-NOV-90	582	PR. 906-371-0
03-DEC-90	583	PR. 906-410002-0/906-369-0/906-410003-0
03-DEC-90	584	NEW SUB-INVESTIGATOR CONTENT: PR. 906-349-4 MCAWEENEY, WILLIAM J., M.D.
11-DEC-90	585	PROTOCOL AMENDMENT CONTENT: AMENDMENT NO. 1 PR. 906-340-15 DATE: 02-JUL-90 ALLOWS FOR THE PROLONGED TREATMENT FOR RESPONDERS OF THIS PROTOCOL.
21-DEC-90	586	SAFETY REPORT CONTENT: PATIENT NO.: NONE (WB) PR. 432-906-600-2045 AE: EXPERIENCED A MYOCARDIAL INFARCTION POSSIBLY DRUG RELATED AE 049-0906-9000005-00
31-DEC-90	587	PR. 906-318 CENTERS 1-7/ 906-430012/ 906-276-25
24-JAN-91		FDA CONTACT MEMO CONTENT: MEMO RE: QUESTIONS ON CHF PROTOCOL (IND SER #587) CONTACT PERSON: SOMANI, PETER, DR. TELEPHONE CALL FROM FDA RE: QUESTIONS REGARDING 906-318. 1: ON P.4, PLEASE CLARIFY TITRATED DOSAGE. 2: PLEASE PROVIDE A RATIONALE FOR DOSE SELECTION (IF 50 MG TID). 3: PROVIDE INFORMATION REGARDING OXYGEN AND CARBON DIOXIDE PARTIAL PRESSURE & AIR FLOW. 4: PROVIDE TREATMILL TIME STATGE.
24-JAN-91		FDA CONTACT MEMO CONTENT: MEMO RE: REQUEST TO OPEN SEPARATE IND FOR CHF INDICATION FOR QUINAPRIL CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO TELEPHONE CALL FROM FDA RE: REQUEST A NEW IND FOR THE CHF INDICATION FOR QUINAPIRL.

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DOC DATE	SER/SUPPL NO	TITLE
25-JAN-91	588	PR. 906-430008-0

DOC DATE	SER/SUPPL NO	TITLE
30-JAN-91		FDA CONTACT MEMO

CONTENT:

MEMO RE: PROVIDED INFORMATION REGARDING CHF
INDICATION FILING
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO
TELEPHONE CALL FROM FDA RE: DR. GRAHAM PROVIDED
AND REQUESTED THE FOLLOWING INFORMATION:
1) NO NEW IND NEEDED FOR THE CHF INDICATION DUE
TO THE LATE STAGE OF DEVELOPMENT.
2) PLEASE PROVIDE OVERVIEW OF THE PROPOSED
SUPPLEMENTAL NDA FOR CHF.
3) PROVIDE A LIST OF STUDIES SEPARATED OUT BY
AREA OF MEDICAL INTEREST.

DOC DATE	SER/SUPPL NO	TITLE
11-FEB-91		FDA CONTACT MEMO

CONTENT:

MEMO RE: FDA WORKSHOP PLANS
CONTACT PERSON: PIERCE, ROSS M.D.
MEETING RE: REQUEST FOR NAME OF THE HELSINKI
INVESTIGATOR INVOLVED IN THE QUANTITATIVE ASPECTS
OF THE LOCAT TRIAL AS WELL AS ANY OTHER EXPERTS
WITH WHOM WE MAY BE WORKING. HE IS PLANNING AND
FDA-SPONSORED WORKSHOP ON METHODOLOGY
STANDARDIZATION IN QUANTITATIVE CORONARY
ANGIOGRAPHY TRIALS.

DOC DATE	SER/SUPPL NO	TITLE
14-FEB-91	589	PR. 906-312 CENTERS 17 - 24

DOC DATE	SER/SUPPL NO	TITLE
21-FEB-91	590	PR. 906-349-14 / NEW PRINCIPLE INVESTIGATOR

CONTENT:

PR. 906-349-9
MITCHELL, WILLIAN M.D.

DOC DATE	SER/SUPPL NO	TITLE
26-FEB-91	591	LETTER RE: RESPONSE TO FDA REQUEST FOR INFORMATION

CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.
CI-906
TO PROVIDE REQUESTED INFORMATION RE:
COMPREHENSIVE LIST OF ALL STUDIES TO BE INCLUDED
IN THE SAFETY DATABASE AND THE LOCATION OF EACH
STUDY PROTOCOL WHICH HAD BEEN SUBMITTED TO THE
IND FILE.
LISTED ARE SEVERAL STUDIES WHICH ARE FOR LOCAL
REGISTRATION PURPOSES IN EUROPE.
PROVIDED A TABULAR SUMMARY WHICH PROVIDES AN
OVERVIEW OF EACH STUDY WHICH WILL HAVE A
FINALIZED STUDY REPORT IN THE SUPPLEMENTAL
APPLICATION.
LIST OF STUDIES CONDUCTED WITH PATIENTS OTHER
THAN THOSE HAVING HYPERTENSION OR CONGESTIVE
HEART FAILURE.
INFORMATION ATTACHED

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DOC DATE	SER/SUPPL NO	TITLE
28-FEB-91	592	LETTER RE: RESPONSE TO FDA REQUEST FOR INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND M.D. CI-906 RE: RESPONDING TO 24-JAN-91 QUESTIONS RECEIVED FROM DR. SOMANI ABOUT THE PROTOCOL 906-318. ANSWERS TO QUESTION ARE ATTACHED.
05-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: IND 3-DAY SAFETY REPORT CONTACT PERSON: CHEN SHAW DR. TELEPHONE CONVERSATION RE: TO ALERT HIM TO A DEATH DUE TO AGRANULATYTOSIS IN A PATIENT TREATED WITH QUINAPRIL. DETAILS OF THIS CASE ARE ATTACHED. WE WOULD PROVIDE WRITTEN REPORT .
08-MAR-91	593	NEW SUB-INVESTIGATOR / STUDY CANCELED
CONTENT:		PR. 906-311-6 COLQUHOUN, M. DR. PR. 906-349-6 STUDY HAS BEEN CANCELED, NO PATIENTS WERE ENROLLED
12-MAR-91	594	SAFETY REPORT
CONTENT:		PATIENT NO.: NOT SPECIFIED (N.S.) PR. 906 FRENCH POST-MARKETING STUDY AE: PATIENT DIED AS A RESULT OF AGRANULOCYTOSIS AE 033-0906-910003-00
25-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: QUINAPRIL NDA CONTACT PERSON: TEMPLE, ROBERT DR. VIA TELEPHONE SUMMARY: ON MAR-25-91 I RECEIVED A TELEPHONE CALL FROM DR. ROBERT TEMPLE REGARDING THE QUINAPRIL PHARMACOLOGY REVIEW. I HAD LEFT A MESSAGE WITH HIS SECRETARY ON MAR-22-91 STATING THAT WE HAD HEARD DR. VAN ARSDALE HAD NOT YET FINISHED HIS REVIEW. BOB SAID THAT DR. VAN ARSDALE HAD COMPLETED THE REVIEW AND WAS DISCUSSING IT WITH HIS SUPERVISOR, DR. RESNICK. HE EXPECTED THAT DR. LIPICKY WOULD HAVE IT SHORTLY. HE SAID HIS REVIEW TIME SHOULD NOT BE LONG DEPENDING UPON OTHER THINGS ON HIS DESK. HE COMMENTED THAT HE WAS PRETTY FAMILIAR WITH THE ACE INHIBITORS AND IT SHOULD NOT BE ANY PROBLEM.

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DOC DATE	SER/SUPPL NO	TITLE
28-MAR-91	595	PR. 906-349-13 / PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-349-13 DATE: 22-MAR-91 ADDS ADDITIONAL ASSESSMENTS FOR PATIENTS SAFETY BY MEASURING SERUM CREATININE TWICE DURING THE FIRST WEEK OF THE DOUBLE-BLIND PHASE OF THE STUDY.		
08-APR-91	596	PR. 906-276 CENTERS 30 AND 33
CONTENT: CENTER NUMBER 33 WILL PARTICIPATE IN BOTH THE OPEN-LABEL AND DOUBLE BLIND PORTION OF THIS STUDY.		
18-APR-91		FDA CONTACT MEMO
CONTENT: MEMO RE: QUESTIONS CONCERNING PROTOCOL 906-43008-0 (SER. NO. 588, JANUARY 25, 1991) CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE SUMMARY: MS. BONGIOVANNI CALLED CONCERNING THE ABOVE PROTOCOL WHICH IS A STUDY OF THE RENAL AND METABOLIC EFFECTS OF QUINAPRIL IN NORMOTENSIVE PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS. THE MEDICAL REVIEWER AND STATISTICIAN AT FDA HAVE SOME CONCERNS ABOUT ENDPOINTS AND SAMPLE SIZE. (THESE WERE NONSPECIFIC CONCERNS AT THIS POINT; HOWEVER, MS. BONGIOVANNI SUGGESTED A MEETING TO DISCUSS.) MS. BONGIOVANNI ASKED IF THE STUDY HAD STARTED YET, TO WHICH I TOLD HER I THOUGHT THAT IT HAD. SHE ASSUMED THAT THIS WAS A STUDY TO SUPPORT A NEW INDICATION, TO WHICH I RESPONDED THAT IT WAS NOT FOR THAT PURPOSE AT ALL. SHE BELIEVED THIS MIGHT CHANGE THEIR CONCERN SOMEWHAT, BUT WANTED TO KNOW A LITTLE MORE ABOUT WHY WE WERE DOING THE STUDY. I SAID I WOULD FIND OUT MORE AND RETURN THE CALL.		
18-APR-91	597	PR. 906-276-32
CONTENT: CENTER NUMBER 32 WILL PARTICIPATE IN BOTH THE OPEN-LABEL AND DOUBLE-BLIND PORTION OF THIS STUDY.		
24-APR-91		FDA CONTACT MEMO
CONTENT: MEMO RE: FOLLOW-UP TO QUESTIONS CONCERNING 906-43008-0 (SEE CONTACT OF APR-18-91). CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE SUMMARY: I CALLED MS. BONGIOVANNI TO FOLLOW-UP ON QUESTIONS RECIEVED CONCERNING PROTOCOL 906-43008-0 ON APRIL 18, 1991. I ASSURED MS. BONGIOVANNI THAT WE WERE NOT PURSUING AN INDICATION IN NORMOTEN- SIVE DIABETIC PATIENTS. WE VIEW THIS PROTOCOL AS A PILOT STUDY. WE FELT THAT THE ORIGINAL PROPOSAL, BY A WELL-KNOWN RESEARCHER IN THE U.K., WAS A REASONABLE AVENUE OF RESEARCH AND SAW NO REASON NOT TO DO A PILOT STUDY. THE REASON THE STUDY WAS		

INCLUDED IN THE U.S. IND WAS A CLINICAL SUPPLIES
SOURCING ISSUE; THE 2.5 MG TABLETS WERE NOT
AVAILABLE FROM EX - U.S. SOURCES. SHE THANKED ME
FOR THE INFORMATION AND SEEMED SATISFIED WITH
OUR RESPONSE.

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DOC DATE	SER/SUPPL NO	TITLE
26-APR-91	598	PR. 906-311-031
CONTENT:		CENTER 31 WILL ALSO PARTICIPATE IN THE OPEN-LABEL PORTION OF THIS STUDY.
26-APR-91	598	NEW SUBINVESTIGATOR / CHANGE IN PROTOCOL
CONTENT:		PR. 906-311-4 SUBINVESTIGATOR LYNCH, S. DR. B.SC, MB, CH.B., MRCGP ON APRIL 8, 1991 (SERIAL NO. 596) WE NOTIFIED YOU OF PROTOCOL 906-276-30. THIS CENTER WILL NOW PARTICIPATE IN THE OPEN-LABEL PORTION OF THIS MULTICENTER STUDY.
17-MAY-91	599	SAFETY REPORT
CONTENT:		PATIENT NI. 001 (EB) PR. 432-906-600-1367 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910005-00
17-MAY-91	599	SAFETY REPORT
CONTENT:		PATIENT NO. 04 (CK) PR. 423-906-600-0942 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910008-00
23-MAY-91	600	SAFETY REPORT
CONTENT:		PATIENT NI. 001 (EB) PR. 432-906-600-1367 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910005-00 FOLLOW-UP SER. NO. 599
23-MAY-91	600	SAFETY REPORT
CONTENT:		PATIENT NO. 04 (CK) PR. 423-906-600-0942 AE: HOSPITALIZED FOR HYPERTENSIVE CRISIS AE NO. 049-0906-910008-00 FOLLOW-UP SER. NO. 599

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23-MAY-91 601 PR. 906-423352 CENTERS 1, 5, AND 7

CONTENT:

ON APRIL 26, 1991 (SERIAL NO. 598) WE
INADVERTENTLY MISNUMBERED OUR PROTOCOL 906-311-31.
THE CORRECT NUMBER IS 906-276-31.

05-JUN-91
CONTENT:

LETTER RE: IND AMENDMENT

LETTER TO: SPIVEY, R.
LETTER FROM: LIPICKY, R. M.D.
RE: PLEASE REFER TO YOUR NEW DRUG APPLICATION
(IND) SUBMITTED UNDER SECTION 505(I) OF THE
FEDERAL FOOD, DRUG, AND COSMETIC ACT FOR ACCUPRIL
(QUINAPRIL HYDROCHLORIDE) TABLETS.
WE ALSO REFER TO YOUR AMENDMENT DATED JAN. 25,
1991, SERIAL NUMBER 588.
WE HAVE COMPLETED OUR REVIEW OF THE PROTOCOL
ENTITLED, "A THREE-YEAR, DOUBLE-BLIND, PARALLEL-
GROUP, PLACEBO-CONTROLLED STUDY TO ASSESS THE
RENAL AND METABOLIC EFFECTS OF ACCUPRO (QUINAPRIL)
IN NORMOTENSIVE PATIENTS WITH NON-INSULIN
DEPENDENT DIABETES MELLITUS."
SHOULD YOU DECIDE TO PURSUE AN INDICATION OF THIS
TYPE, WE ADVISE YOU TO MEET WITH THE DIVISION TO
DISCUSS YOUR CLINICAL DEVELOPMENT PLANS. IN
DESIGNING TRIALS TO DEMONSTRATE PRESERVATION OF
RENAL FUNCTION, -----
CONTINUED - SEE CENTRAL FILE COPY.

11-JUN-91 602
CONTENT:

RESPONSE TO FDA REQUEST FOR INFORMATION

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: SPIVEY, RICHARD PHARM.D., PH.D.
RE: RESPONSE TO FDA REQUEST FOR INFORMATION
REFERENCE IS MADE TO YOUR LETTER OF JUNE 5, 1991
AND TO OUR AMENDMENT OF JANUARY 25, 1991 (SERIAL
NO. 588). THANK-YOU FOR YOUR COMMENTS REGARDING
THE PROTOCOL SUBMITTED IN THE ABOVE REFERENCED
AMENDMENT.
WE ARE NOT CURRENTLY PURSUING AN INDICATION FOR
QUINAPRIL IN THE TREATMENT OF NORMOTENSIVE
PATIENTS WITH NON-INSULIN DEPENDENT DIABETES
MELLITUS. SHOULD WE DECIDE TO PURSUE AN
INDICATION OF THIS TYPE WE WILL CONTACT THE
DIVISION TO DISCUSS OUR CLINICAL DEVELOPMENT
PLANS.
IF YOU HAVE ANY ADDITIONAL COMMENTS OR QUESTIONS
PLEASE CONTACT ME AT (313) 996-7061.

CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO.	TITLE
21-JUN-91	603	INFORMATION AMENDMENT
CONTENT:		
		RR 764-01579 AUTHORS: OLSON, S. ET AL DATE: 17-SEP-90 "DISTRIBUTION OF 14C-CI-906 IN TISSUE OF PREGNANT RATS FOLLOWING SINGLE ORAL DOSE"
		RR 745-01754 AUTHOR: BLEAVINS, M.R. DATE: 02-FEB-91 "IN VITRO ANALYTICAL INTERFERENCE TESTING OF CI-906, CI-975, AND CI-9033"
		RR 740-02922 AUTHOR: TAYLOR, D.G. DATE: 30-JAN-91 "QUINAPRIL AND THE PREVENTION OF GENETIC HYPER- TENSION IN THE SPONTANEOUSLY HYPERTENSIVE RAT"
21-JUN-91	603	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
		RR 740-02947 AUTHORS: KEISER, J.A. ET AL DATE: 15-APR-91 "COMPARISON OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS: EFFECTS ON RENAL FUNCTION IN THE SALT-DEPLETED RAT"
		RR 740-02895 AUTHORS: KEISER, J.A. ET AL DATE: 17-APR-91 "ANTIHYPERTENSIVE EFFECTS OF IV OR ORALLY ADMINISTERED DILTIAZEM IN QUINAPRIL-TREATED SPONTANEOUSLY HYPERTENSIVE RATS"
21-JUN-91	603	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
		RR 740-02936 AUTHORS: BJORK, F. AND KEISER, J. DATE: 03-JUN-91 "VASCULAR BED SELECTIVITY STUDIES WITH QUINAPRIL, CAPTOPRIL, AND ENALAPRIL IN ANESTHETIZED MONGREL DOGS"
		RR 720-02833 AUHTORS: CANTER D.E. ET AL DATE: 02-NOV-90 "A 36-WEEK, OPEN-LABEL EXTENSION OF A 16-WEEK, DOUBLE-BLIND, OPTIONAL-TITRATION, MULTICENTER STUDY COMPARING THE EFFICACY OF ONCE DAILY QUINAPRIL HYDROCHLORIDE WITH TWICE DAILY PROPRANOLOL IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION (PROTOCOL 906-183X)"

CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE SER/SUPPL NO TITLE

21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR 720-02839

AUTHORS: CANTER, D.A. ET AL

DATE: 09-NOV-90

"INITIAL SUMMARY OF RESULTS ON THE DOSE RESPONSE
RELATIONSHIP, HUMORAL EFFECTS AND
PHARMACOKINETICS OF QUINAPRIL IN SALT-REPLETE
NORMOTENSIVE SUBJECTS (PROTOCOL 906-296)"

RR 4301-00062

AUTHORS: WOELFING A. AND LILIENTHAL, J.

DATE: 15-FEB-91

"REPORT OF A 12-WEEK, UNCONTROLLED, OPEN-LABEL
STUDY TO DETERMINE THE EFFICACY AND SAFETY OF
ONCE DAILY ORALLY ADMINISTERED QUINAPRIL
HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO
MODERATE HYPERTENSION (PROTOCOL 906-246)"

21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR 4301-00063

AUTHORS: LILIENTHAL, J. AND WOELFING, A.

DATE: 15-FEB-91

"REPORT OF A 12-WEEK, UNCONTROLLED, OPEN-LABEL
STUDY TO DETERMINE THE EFFICACY AND SAFETY OF
ONCE DAILY ORALLY ADMINISTERED QUINAPRIL
HYDROCHLORIDE (CI-906) WHEN ADDED TO
HYDROCHLOROTHIAZIDE 25 MG ONCE A DAY IN PATIENTS
WITH MODERATE TO SEVERE HYPERTENSION (PROTOCOL
906-247)"

21-JUN-91 603 INFORMATION AMENDMENT - CONTINUED
CONTENT:

RR 724-00129

AUTHORS: SEDMAN, A. ET AL

DATE: 05-APR-91

"A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED,
MULTIPLE-DOSE STUDY OF THE HEMODYNAMIC EFFECTS OF
QUINAPRIL HCL (CI-906) IN PATIENTS WITH MILD TO
MODERATE HYPERTENSION (PROTOCOL 906-293)"

RR 744-00040

AUTHORS: BMMERT, J.A. ET AL

DATE: 28-APR-91

"MULTIPLE-DOSE PHARMACOKINETICS OF QUINAPRIL AND
ITS ACTIVE METABOLITE QUINAPRILAT IN PATIENTS
WITH CONGESTIVE HEART FAILURE: PROTOCOL 906-256"

REGULATORY LIAISON AND COMPLIANCE
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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
21-JUN-91	603	INFORMATION AMENDMENT - CONTINUED
CONTENT: ALL SAFETY DATA FROM CLINICAL STUDIES HAVE BEEN INCORPORATED IN THE QUINAPRIL THIRD SAFETY UPDATE TO NDA 19-885 (19-FEB-91). THE RESULTS OF THE STUDIES INCLUDED IN THIS SUBMISSION DO NOT EFFECT THE CONCLUSION REPORTED IN OUR PENDING NDA 19-885.		
21-JUN-91	604	PR. 906-371-2
09-JUL-91	605	ANNUAL REPORT
CONTENT: ISSUE DATE: 01-JUL-91		
16-JUL-91	606	PR. 906-423352 CENTERS 2, 3, 4 AND 6
16-JUL-91	606	PROTOCOL AMENDMENT
CONTENT: AMENDMENT NO. 1 PR. 906-371-0 DATE: 23-APR-91 THIS AMENDMENT CHANGES THE PROTOCOL TITLE TO ALLOW COMPASSIONATE USE OF QUINAPRIL FOR PATIENTS PREVIOUSLY AND OR CURRENTLY IN QUINAPRIL CHF CLINICAL TRIALS FOR WHOM THE USE OF CURRENTLY AVAILABLE MARKETED ACE-INHIBITOR THERAPIES IS CONTRAINDICATED, INEFFECTIVE OR CAUSES INTOLERABLE SIDE EFFECTS.		

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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE SER/SUPPL NO TITLE

01-AUG-91
CONTENT:

607

SAFETY REPORT

PATIENTS NO. 004/ES
PR. 423-900-600-0587
AE: ASTHMATIC BRONCHITIS AFTER APPROXIMATELY TWO
MONTHS OF QUINAPRIL; PATIENT SUBSEQUENTLY
RECOVERED.
AE. NO. 049-0906-910027-00

06-AUG-91
CONTENT:

608

LETTER RE: INFORMATION AMENDMENT; CLINCIAL

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: SPIVEY, RICHARD
RE: REFERENCE IS MADE TO AN ORIGINAL WRITTEN
SAFETY REPORT FOR ACCUPRIL (QUINAPRIL
HYDROCHLORIDE) TABLETS SUBMITTED 01-AUG-91 (SER.
NO. 607). WE ARE PROVIDING, FOR YOUR INFORMATION,
A COPY OF THE LETTER WHICH WAS SENT TO
INVESTIGATORS, NOTIFYING THEM OF A REPORT OF
ASTHMATIC BRONCHITIS.
PLEASE INCORPORATE THIS INFORMATION, BY CROSS-
REFERENCE, INTO OUR PENDING NDA 19-885 FOR
ACCUPRIL. SHOULD YOU HAVE QUESTIONS-----

20-AUG-91
CONTENT:

609

SAFETY REPORT

PATIENT NO. 007/CHE
PR. 955-5-23
AE: 38 YEAR OLD MALE WHO EXPERIENCED DIARRHEA,
VOMITING AND FEVER RESULTING IN DEHYDRATION AND
RENAL FAILURE.
AE NO. 033-0955-910002-00

REGULATORY LIAISON AND COMPLIANCE
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CI NUMBER= 906 APPL NUMBER= 20,336

DOC DATE	SER/SUPPL NO	TITLE
13-SEP-91	610	SAFETY REPORT
CONTENT:		
PATIENT NO.: /ED		
PR. 906-		
AE: AUTOIMMUNE HEMOLYTIC ANEMIA		
AE. NO. 033-0906-910010-00		
26-SEP-91	611	PR. 906-375-0
26-SEP-91	612	LETTER RE: INFORMATION AMENDMENT CLINICAL
CONTENT:		
LETTER TO: LIPICKY, RAYMOND MD		
LETTER FROM: SPIVEY, RICHARD		
RE: REFERENCE IS MADE TO AN ORIGINAL WRITTEN		
SAFETY REPORT FOR ACCUPRIL (QUINAPRIL HYDRO-		
CHLORIDE) TABLETS SUBMITTED 13-SEP-91 (SER# 610).		
WE ARE PROVIDING, FOR YOUR INFORMATION, A COPY OF		
THE LETTER WHICH WAS SENT TO INVESTIGATORS,		
NOTIFYING THEM OF A REPORT OF HEMOLYTIC ANEMIA.		
QUESTIONS CALL-----		
16-OCT-91	613	INFORMATION AMENDMENT
CONTENT:		
RR 744-00033		
AUTHORS: BURGER, P.J. ET AL		
DATE: 13-JUN-91		
"A PHARMACOKINETIC STUDY TO DETERMINE WHETHER 10-		
MG AND 20-MG QUINAPRIL HCL TABLETS MANUFACTURED		
IN VEGA BAJA, PUERTO RICO USING FLUID BED DRYING		
ARE BIOEQUIVALENT TO 20-MG QUINAPRIL TABLETS		
MANUFACTURED IN MORRIS PLAINS, NEW JERSEY USING		
OVEN-DRIED GRANULATION: PROTOCOL 906-346"		
16-OCT-91	613	INFORMATION AMENDMENT - CONTINUED
CONTENT:		
RR 4301-00087		
AUTHOR: WOELFING, A.		
DATE: 17-JUN-91		
"REPORT OF A 12-WEEK, UNCONTROLLED, OPEN-LABEL		
STUDY TO DETERMINE THE EFFICACY AND SAFETY OF		
ONCE DAILY 20 MG OR 40 MG ORALLY ADMINISTERED		
QUINAPRIL HYDROCHLORIDE (CI-906) OR 40 MG		
QUINAPRIL HYDROCHLORIDE COMBINED WITH		
HYDROCHLORITHIAZIDE 25 MG (CI-955) ONCE A DAY IN		
PATIENTS WITH MILD TO MODERATE HYPERTENSION		
(PROTOCOL 906-253)"		

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16-OCT-91 613 PROTOCOL AMENDMENT

CONTENT:

AMENDMENT NO. 2
PR. 906-351-0
DATE: 12-AUG-91
AMENDMENT CHANGES THE INCLUSION CRITERIA AND SOME
LABORATORY DETERMINATIONS.

31-OCT-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: QUESTIONS ON PROTOCOL 906-276
CONTACT PERSON: KENNEMER, E. VIA TELEPHONE
MEMO FROM: SPIVEY, R.
ABSTRACT: QUESTIONS ON PROTOCOL 906-276.

13-NOV-91 614 IB UPDATE

CONTENT:

DATE: 09-MAY-89 (REVISED 27-SEP-91)
RR X-720-02572
AUTHORS: DAWKINS, R. AND PURCELL, T.J.
"INVESTIGATOR'S BROCHURE: QUINAPRIL HYDROCHLORIDE
(CI-906)"
REVISED: 25-OCT-91
THE INFORMATION FOR INVESTIGATOR'S SECTION (PAGES
2-14) HAS BEEN UPDATED GENERALLY, AND NOW INCLUDES
ADDITIONAL INFORMATION ON THE USE OF QUINAPRIL IN
THE TREATMENT OF CONGESTIVE HEART FAILURE.

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CI NUMBER= 906 APPL NUMBER= 19-885

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26-JAN-89 1 INITIAL NDA
CONTENT:

VOLUMES=286
ITEM 1: OVERALL DETAILED INDEX TO NDA 19-885.
ITEM 2: COMPREHENSIVE SUMMARY.
ITEM 3: CHEMISTRY, MANUFACTURING AND CONTROLS.
ITEM 4: SAMPLES, METHODS VALIDATION AND LABELING.
ITEM 5: NON CLINICAL PHARMACOLOGY AND TOXICOLOGY.

RR 740-00929
AUTHOR: KAPLAN, H.R.
DATE: 30-MAR-82
"THE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME
(ACE) INHIBITORS CI-906 AND CI-907 ON ARTERIAL
BLOOD PRESSURE AND HEART RATE IN CONSCIOUS RENAL
HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-00930
AUTHOR: KAPLAN, H.R.
DATE: 12-MAR-82
"SUBACUTE EFFECTS OF ANGIOTENSIN CONVERTING
ENZYME (ACE) INHIBITOR CI-906 ON BLOOD PRESSURE
AND HEART RATE IN CONSCIOUS RENAL HYPERTENSIVE
RATS: A FIVE-DAY STUDY"

RR 740-02483
AUTHOR: RYAN, M.J.
DATE: 7-JUN-88
"ANTIHYPERTENSIVE EFFECTS OF QUINAPRIL DURING A
FIVE-DAY DOSING STUDY IN RENAL HYPERTENSIVE RATS"

RR 740-02484
AUTHOR: RYAN, M.J.
DATE: 7-JUN-88
"ANTIHYPERTENSIVE ACTIVITY OF QUINAPRIL IN
HYDROCHLOROTHIAZIDE-TREATED CONSCIOUS
SPONTANEOUSLY HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-00931
AUTHOR: KAPLAN, H.R. ET AL
DATE: 13-APR-82
"EFFECTS OF ANGIOTENSIN CONVERTING ENZYME (ACE)
INHIBITORS CI-906 AND CI-907 ON ARTERIAL BLOOD
PRESSURE AND HEART RATE IN CONSCIOUS
SPONTANEOUSLY HYPERTENSIVE RATS (SHR): A FIVE-
DAY STUDY"

RR 740-00936
AUTHORS: SINGER, R.
RYAN, M.
DATE: 23-MAR-82
"PRELIMINARY EVALUATION OF THE ANTIHYPERTENSIVE
EFFECTS OF ANGIOTENSIN CONVERTING ENZYME
INHIBITORS IN DEHYDRATED HYPERTENSIVE DOGS"

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CI NUMBER= 906 APPL NUMBER= 19-885

DOC DATE	SER/SUPPL NO	TITLE
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00938 AUTHORS: SINGER, R. RYAN, M. DATE: 31-MAR-82 "BLOOD PRESSURE LOWERING ACTIVITY OF A NEW NONSULFHYDRYL ANGIOTENSIN CONVERTING ENZYME INHIBITORS, CI-906: COMPARISON WITH MK-421"</p> <p>RR 740-02378 AUTHOR: SINGER, R. ET AL DATE: 16-DEC-87 "EFFECTS OF QUINAPRIL ON BLOOD PRESSURE AND HEART RATE IN DIURETIC-TREATED RENAL HYPERTENSIVE DOGS"</p> <p>RR 740-02377 AUTHOR: SINGER, R. DATE: 4-JAN-88 "EFFECTS OF ENALAPRIL ON BLOOD PRESSURE AND HEART RATE IN DIURETIC-TREATED RENAL HYPERTENSIVE DOGS"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00271 AUTHOR: PARKER, R.B. DATE: 13-FEB-79 "METHOD: IN VITRO (BIOCHEMICAL) ASSAY FOR ANGIOTENSIN CONVERTING ENZYME (ACE) AND THE INHIBITION OF ACE"</p> <p>RR 740-00610 AUTHORS: ESSENBURG, A.D. SMITH, R.D. DATE: 28-APR-81 "CN-109,452 INHIBITION OF GUINEA PIG SERUM ANGIOTENSIN CONVERTING ENZYME (ACE) ACTIVITY IN VITRO"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00935 AUTHORS: ESSENBURG, A.D. COHEN, D.M. DATE: 30-MAR-82 "IN VITRO INHIBITION OF ANGIOTENSIN CONVERTING ENZYME ACTIVITY WITH CI-906 IN PLASMA FROM NORMOTENSIVE AND HYPERTENSIVE HUMANS"</p> <p>RR 740-00704 AUTHORS: MAJOR, T.C. COHEN, D.M. DATE: 13-APR-82 "THE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS (ND-92275, CN-108182, CN-109326, CN-109325, CN-109452-2K, CN-109438-2, CN-109762-2, AND CN-110021-1A) ON TENSION</p>

DEVELOPMENT IN ISOLATED RABBIT AND RAT AORTIC
CIRCULAR TISSUE SEGMENTS"

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CI NUMBER= 906 APPL NUMBER= 19-885

DOC DATE	SER/SUPPL NO	TITLE
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00706 AUTHOR: SMITH, R.D. ET AL DATE: 17-AUG-81 "EFFECT OF NC-109,452-2, MK-421, AND CAPTORIL ON THE RESPONSES TO ANGIOTENSIN I, ANGIOTENSIN II, NOREPINEPHRINE AND BRADYKININ IN CONSCIOUS NORMOTENSIVE RATS"</p> <p>RR 740-00880 AUTHOR: METZ, T.E. ET AL DATE: 14-JAN-82 "COMPARISON OF THE EFFECTS OF CI-906, CI-907, CAPTOPRIL, AND MK-421 ON THE RESPONSES TO ANGIOTENSIN I, ANGIOTENSIN II, NOREPINEPHRINE, AND BRADYKININ IN CONSCIOUS, NORMOTENSIVE RATS"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-00934 AUTHOR: COHEN, D.M. ET AL DATE: 17-MAR-82 "CORRELATION OF PLASMA ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITION WITH ANTIHYPERTENSIVE EFFECTS OF CI-906 AND MK-421 (NC-109326-6614) IN RENAL HYPERTENSIVE RATS"</p> <p>RR 740-00995 AUTHOR: COHEN, D.M. ET AL DATE: 10-AUG-82 "CORRELATION OF AORTIC AND BRAIN ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITION WITH ANTIHYPERTENSIVE EFFECTS OF CI-906, AND MK-421 (CN-109326-6614) IN RENAL HYPERTENSIVE RATS"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 740-01803 AUTHOR: COHEN, D.M. DATE: 22-OCT-85 "EFFECTS OF SEVERAL ACE INHIBITORS ON BRAIN CONVERTING ENZYME ACTIVITY IN NORMOTENSIVE RATS"</p> <p>RR 740-00837 AUTHOR: SODERBERG, V. ET AL DATE: 31-MAR-82 "ORAL ANGIOTENSIN CONVERTING ENZYME INHIBITORY ACTIVITY OF CI-906 IN THE CONSCIOUS DOG; COMPARISON WITH MK-421 (ENALAPRIL) AND CAPTOPRIL (SQ-14,225)"</p>

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CI NUMBER= 906 APPL NUMBER= 19-885

DOC DATE SER/SUPPL NO TITLE

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-01372

AUTHORS: GERMAIN, C.L.
MERTZ, T.E.

DATE: 24-APR-84

"COMPARISON OF THE EFFECTS OF CI-906, CAPTOPRIL,
AND ENALAPRIL (ACE INHIBITORS) ON THE BLOOD
PRESSURE AND HEART RATE RESPONSES TO BRADYKININ
BEFORE AND AFTER TREATMENT WITH INDOMETHACIN IN
CONSCIOUS RABBITS"

RR 740-02519

AUTHOR: PACE, D.P. ET AL

DATE: 30-AUG-88

"HEMODYNAMIC RESPONSES TO QUINAPRIL (CI-906) IN
CONSCIOUS SODIUM-RESTRICTED FUROSEMIDE-TREATED
DOGS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-00792

AUTHOR: POTOCZAK, R.E. ET AL

DATE: 15-SEP-81

"THE EFFECTS OF CI-906 ON CARDIOVASCULAR FUNCTION
IN NORMAL CONSCIOUS DOGS"

RR 740-00793

AUTHOR: POTOCZAK, R.E. ET AL

DATE: 15-SEP-81

"THE EFFECTS OF MK-421 ON CARDIOVASCULAR FUNCTION
IN NORMAL CONSCIOUS DOGS"

RR 740-00502

AUTHOR: POTOCZAK, R.E. ET AL

DATE: 19-MAY-80

"THE EFFECTS OF CAPTOPRIL ON CARDIOVASCULAR
FUNCTION IN NORMAL CONSCIOUS DOGS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-02158

AUTHORS: STEFFEN, R.P.
ELDON, C.M.

DATE: 3-MAR-87

"THE HEMODYNAMIC EFFECTS OF THE ANGIOTENSIN
CONVERTING ENZYME INHIBITOR, CI-928 IN A MODEL
OF ACUTE PROPRANOLOL INDUCED HEART FAILURE IN
THE ANESTHETIZED DOG"

RR 740-02520

AUTHOR: KEISER, J.A.

DATE: 22-AUG-88

"THE EFFECTS OF ACUTE INTRAVENOUS ADMINISTRATION
OF QUINAPRIL AT OR VEHICLE ON RENAL FUNCTION IN
ANESTHETIZED MORGREL DOGS"

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CI NUMBER= 906 APPL NUMBER= 19-885

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-02345 AUTHORS: STEFFEN, R.P. ELDON, C.M. DATE: 11-DEC-87 "EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS ON RENAL AND PERIPHERAL HEMODYNAMICS AND URINE OUTPUT IN ANESTHETIZED DOG"
		RR 740-00932 AUTHOR: KAPLAN, H.R. ET AL DATE: 12-MAR-82 "SUBACUTE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR CI-906 ON BLOOD PRESSURE AND HEART RATE IN CONSCIOUS NORMOTENSIVE RATS: A SEVEN-DAY STUDY"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR MEMO-740-00637 AUTHOR: STUCKI, W.P. DATE: 28-APR-81 "EX VIVO PLATELET AGGREGATION STUDIES ON CN-109452-2"
		RR 740-00713 AUTHOR: UHLENDORF, P.D. DATE: 18-MAY-81 "LIPID REGULATING EFFECT OF THE ANTIHYPERTENSIVE AGENT CN-109,452"
		RR 740-01706 AUTHOR: UHLENDORF, P.D. ET AL DATE: 30-JUN-86 "LIPID-REGULATING EFFECT OF CI-906, CI-907, AND CI-925 IN CHOLESTEROL-FED RATS: COMPARISON TO REFERENCE ACE INHIBITORS"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-02001 AUTHOR: KRAUSE, B. ET AL DATE: 14-NOV-86 "THE EFFECT OF QUINAPRIL ON PLASMA LIPID CONCENTRATIONS IN NORMAL RATS: COMPARISON TO REFERENCE ACE INHIBITORS"
		RR 740-02456 AUTHOR: KRAUSE, B.R. ET AL DATE: 6-JUN-88 "EFFECT OF QUINAPRIL, CAPTOPRIL, AND ENALAPRIL IN FRUCTOSE-FED RATS"
		RR 740-01931 AUTHOR: KRAUSE, B. ET AL DATE: 1-III-86

"THE EFFECTS OF BEVANTOLOL ON PLASMA LIPID
CONCENTRATIONS IN NORMAL RATS: COMPARISON TO
REFERENCE ANTIHYPERTENSIVE AGENTS"

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CI NUMBER= 906 APPL NUMBER= 19-885

DOC DATE	SER/SUPPL NO	TITLE
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-02528
		AUTHOR: KRAUSE, B.R. ET AL
		DATE: 2-AUG-88
		"EFFECT OF ACE INHIBITORS ON PLASMA LIPIDS IN NORMAL RATS: CONFIRMATION OF TRIGLYCERIDE- LOWERING EFFECT USING ORAL DOSING"
		RR 740-00940
		AUTHORS: BURMEISTER, W.E.
		KAPLAN, H.R.
		DATE: 16-APR-82
		"THE EFFECTS OF CI-906, MK-421, AND CAPTOPRIL ON BARORECEPTOR REFLEX HEART RATE RESPONSES IN THE ALPHA-CHLORALASE ANESTHETIZED DOG MODEL"
		RR 740-00646
		AUTHOR: KINKEL, M.
		DATE: 23-MAR-81
		"A PULMONARY SAFETY STUDY WITH INTRAVENOUS CN-109452 IN THE ANESTHETIZED DOG"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-00649
		AUTHORS: FINKEL, M.
		FOSTER, T.
		DATE: 1-JUN-81
		"A PULMONARY RISK ASSESSMENT OF CN-109452-2L"
		RR 740-00742
		AUTHOR: MERTZ, T.E. ET AL
		DATE: 24-JUN-81
		"AUTONOMIC EVALUATION OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITOR ANTIHYPERTENSIVE AGENTS CN-109452, CAPTOPRIL, AND MK 421"
		RR 740-00747
		AUTHOR: MERTZ, T.E ET AL
		DATE: 24-JUN-81
		"SELECTIVE INHIBITION OF ANGIOTENSIN I AND POTENTIATION OF BRADYKININ BY CN-109452, CAPTOPRIL, AND MK421 IN ANESTHETIZED DOGS"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-00666
		AUTHOR: LABAY, R.J. ET AL
		DATE: 4-MAY-81
		"EFFECTS OF CN-109452-2 IN THE CNS SURVEY"
		RR 740-00647
		AUTHORS: WILEY, J.N.
		DOWNES, D.A.
		DATE: 19-MAR-81
		"EVALUATION OF CN-109452-2K IN MOUSE ACTIVITY AND INVERTED SCREEN TEST (MAST)

RR 740-00860

AUTHORS: BOHNER, B.L.
 DOWNS, D.A.

DATE: 30-NOV-81

"THE EFFECT OF CN-109452-2K IN THE PHARMACOLOGICAL
RIST TEST"

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CONTENT:		
		RR 740-00687 AUTHORS: VARTANIAN, M. POSCHER, P. DATE: 4-MAY-81 "EFFECTS OF CN-109452-2L ON CONSUMMATORY BEHAVIOR"
		RR 740-00652 AUTHORS: NINTEMAN, F. SMITH, M. DATE: 4-MAY-81 "THE EFFECT OF CN-109,452-2L ON SELF-STIMULATING RATS"
		RR 740-02311 AUTHOR: DAVIS, R.E. DATE: 3-DEC-87 "EFFECT PD 109452 (CI-906), AN ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACE), ON BODY TEMPERATURE AND SURVIVAL TIME UNDER NORMABARIC HYPOXIA IN MICE"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-02313 AUTHOR: DAVIS, R.E. DATE: 8-DEC-87 "REVERSAL OF ECS-INDUCED AMNESIA BY ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE) IN WEANING RATS"
		RR 740-02312 AUTHOR: DAVIS, R.E. DATE: 3-DEC-87 "EFFECTS OF CI-906 (PD 109452), AN ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACE), ON DELAYED ALTERNATION PERFORMANCE IN RATS"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 740-01319 AUTHOR: WILEY, J.N. ET AL DATE: 9-FEB-84 "EVAUATION OF CI-906, CI-907, AND CI-925, POTENTIAL ACE INHIBITORS, AND REFERENCE DRUGS CAPTOPRIL AND ENALAPRIL IN THE MOUSE ANTIWRITHING TEST"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 740-00698 AUTHOR: COUGHENOUR, L.L. ET AL DATE: 26-JUN-81 "THE AFFINITY OF CN-109452-2 (CI-906) AND CAPTOPRIL FOR VARIOUS NEUROTRANSMITTER RECEPTORS IN RAT BRAIN" RR 740-02301 AUTHORS: WEISHAAR, R.E. ESSENBURG, A.D. DATE: 24-JUL-87 "EFFECT OF PD 127751-2 ON THE ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME" RR 740-02355 AUTHORS: WEISHAAR, R.E. ESSENBERG, A.D. DATE: 4-JAN-88 "EFFECT OF PD 109452-2 AND REFERENCE AGENTS ON THE ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 740-02354 AUTHORS: WIESHAAR, R.E. ESSENBERG, A.D. DATE: 4-JAN-88 "EFFECT OF PD 109489-2K AND REFERENCE AGENTS ON THE ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME" RR 740-02290 AUTHOR: RYAN, M.J. DATE: 24-JUL-87 "THE EFFECTS OF ORAL ADMINISTRATION OF PD 127,751 ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN CONSCIOUS RENAL HYPERTENSIVE RATS" RR 740-02369 AUTHOR: RYAN, M.J. DATE: 13-NOV-87 "THE EFFECTS OF ORAL ADMINISTRATION OF PD 109489-2 ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN CONSCIOUS RENAL HYPERTENSIVE RATS"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 740-02152 AUTHOR: RYAN, M.J. DATE: 24-FEB-87 "THE EFFECTS OF ORAL ADMINISTRATION OF THE ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR CI-928 ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN CONSCIOUS GOLDBLATT HYPERTENSIVE RATS" RR 740-02357 AUTHORS: WEISHAAR, R.E. ESSENBURG, A.D.

DATE: 4-JAN-88

"EFFECT OF PD 118854 AND REFERENCE AGENTS ON THE
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

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CONTENT:

RR 740-02367
AUTHOR: RYAN, M.J. ET AL
DATE: 12-NOV-87
"THE EFFECTS OF ORAL ADMINISTRATION OF PD 118854-2
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN
CONSCIOUS RENAL HYPERTENSIVE RATS"

RR 740-02356
AUTHORS: WEISHAAR, R.E.
ESSENBERG, A.D.
DATE: 4-JAN-88
"EFFECT OF PD 126130 AND REFERENCE AGENTS ON THE
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

RR 740-02368
AUTHOR: RYAN, M.J. ET AL
DATE: 13-NOV-87
"THE EFFECTS OF ORAL ADMINISTRATION OF PD 126130-2
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN
CONSCIOUS RENAL HYPERTENSIVE RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-2291
AUTHORS: WEISHAAR, R.E.
ESSENBERG, A.D.
DATE: 24-JUL-87
"EFFECT OF PD 109488 ON THE ACTIVITY OF
ANGIOTENSIN CONVERTING ENZYME"

RR 740-02353
AUTHORS: WEISHAAR, R.E.
ESSENBERG, A.D.
DATE: 11-DEC-87
"EFFECT OF PD 113413 AND REFERENCE AGENTS ON THE
ACTIVITY OF ANGIOTENSIN CONVERTING ENZYME"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 740-02283
AUTHOR: RYAN, M.J. ET AL
DATE: 14-JUL-87
"THE EFFECTS OF ORAL ADMINISTRATION OF PD 109488
ON ARTERIAL BLOOD PRESSURE AND HEART RATE IN
CONSCIOUS SPONTANEOUSLY HYPERTENSIVE AND RENAL
HYPERTENSIVE RATS"

RR 745-00433
AUTHOR: KIM, S.N. ET AL
DATE: 31-AUG-81
"ACUTE ORAL TOXICITY STUDY OF CI-906 IN MALE AND
FEMALE ALBINO MICE"

RR 250-01303
AUTHOR: BARSOUM, N.J.
DATE: 15-MAR-82

"ACUTE ORAL TOXICITY STUDY OF CI-906
(PD 109452-2) IN MICE"

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RR 250-01332
AUTHOR: BARSOUM, N.J. ET AL
DATE: 26-AUG-83
"ACUTE ORAL TOXICITY STUDY OF CI-906 (PD 109452-2)
IN MICE"

RR 250-01516
AUTHOR: MACALLUM, G.E. ET AL
DATE: 9-NOV-87
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906
(PD 109452-2) IN MICE"

RR MEMO-745-00426
AUTHOR: SANYER, J.L. ET AL
DATE: 25-AUG-81
"PRELIMINARY DOSE RANGE FINDING ACUTE ORAL
TOXICITY STUDY OF CI-906 IN MALE AND FEMALE
ALBINO RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 745-00427
AUTHOR: SANYER, J.L. ET AL
DATE: 28-AUG-81
"ACUTE ORAL TOXICITY STUDY OF CI-906 IN MALE AND
FEMALE ALBINO RATS"

RR 745-00459
AUTHOR: ANDERSON, J.A. ET AL
DATE: 22-JAN-82
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906
IN MALE AND FEMALE ALBINO RATS"

RR 250-01515
AUTHOR: MACALLUM, G.E.
DATE: 9-NOV-87
"ACUTE INTRAVENOUS TOXICITY STUDY OF CI-906
(PD 109452-2) IN RATS:

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 745-00441
AUTHOR: WATKINS, J.R. ET AL
DATE: 27-OCT-81
"EXPLORATORY ORAL RISING DOSE STUDY IN BEAGLE
DOGS WITH CI-906"

RR 250-01338
AUTHOR: BARSOUM, N.J. ET AL
DATE: 2-DEC-83
"14 DAY REPEATED DOSE ORAL TOXICITY STUDY OF
CI-906 IN MICE"

RR 745-00779
AUTHOR: LAVACEVADA, M. II ET AL

DATE: 5-DEC-84
"THIRTEEN-WEEK MOUSE ORAL RANGE FINDING STUDY:
CI-906"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 745-00333 AUTHOR: SANYER, J.L. ET AL DATE: 3-MAR-82 "TWO-WEEK EXPLORATORY ORAL TOXICITY STUDY OF CI-906 IN MALE AND FEMALE ALBINO RATS" RR 745-00479 AUTHOR: WATKINS, J.R. ET AL DATE: 4-MAR-82 "TWO WEEK ORAL TOXICITY STUDY OF CI-906 IN MALE AND FEMALE ALBINO RATS" RR 745-00552 AUTHOR: KIM, S.N. ET AL DATE: 29-DEC-82 "THIRTEEN-WEEK ORAL TOXICITY STUDY OF CI-906 IN MALE AND FEMALE ALBINO RATS"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 745-00686 AUTHOR: ANDERSON, J.A. ET AL DATE: 16-APR-84 "52-WEEK ORAL TOXICITY STUDY AND 104-WEEK CARCINOGEN BIOASSAY OF CI-906 IN RATS - 26-WEEK SUMMARY REPORT" RR 745-00776 AUTHOR: ANDERSON, J.A. ET AL DATE: 18-DEC-84 "52-WEEK ORAL TOXICITY STUDY AND 104-WEEK CARCINOGEN BIOASSAY OF CI-906 IN RATS - 52-WEEK SUMMARY REPORT" RR 745-00460 AUTHOR: MCGUIRE, E.J. ET AL DATE: 25-FEB-82 "TWO-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 745-00539 AUTHOR: ANDERSON, J.A. ET AL DATE: 20-DEC-82 "13-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS" RR 745-00716 AUTHOR: JAYASEKARA, M.U. ET AL DATE: 14-MAY-84 "52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE DOGS - 26-WEEK SUMMARY REPORT"

AUTHOR: JAYASEKARA, M.U. ET AL

DATE: 18-DEC-84

"52-WEEK ORAL TOXICITY STUDY OF CI-906 IN BEAGLE
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		RR 745-00749 AUTHOR: ANDERSON, J.A. ET AL DATE: 17-SEP-84 "FERTILITY AND REPRODUCTION STUDIES IN RATS WITH CI-906"
		RR 745-00541 AUTHOR: ANDERSON, J.A. ET AL DATE: 9-DEC-82 "TERATOLOGY STUDY IN RATS WITH CI-906"
		RR 745-00527 AUTHOR: KIM, S.N. ET AL DATE: 1-OCT-82 "EXPLORATORY DOSE RANGE-FINDING STUDY IN RABBITS WITH CI-906"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 745-00608 AUTHOR: ANDERSON, J.A. ET AL DATE: 20-JUN-83 "EXPLORATORY RANGE-FINDING TERATOLOGY STUDY IN RABBITS WITH CI-906"
		RR 745-00639 AUTHOR: ANDERSON, J.A. ET AL DATE: 11-OCT-83 "TERATOLOGY STUDY IN RABBITS (CI-906)"
		RR 745-00844 AUTHOR: ANDERSON, J.A. DATE: 13-SEP-85 "PERINATAL AND POSTNATAL STUDY IN RATS WITH CI-906"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 745-00412 AUTHOR: LAKE, R.S. ET AL DATE: 29-MAY-81 "STANDARD BACTERIAL MUTAGENICITY PLATE ASSAY OF CN-109452"
		RR 745-00523 AUTHOR: ANDERSON, J.A. ET AL DATE: 2-AUG-82 "IN VITRO POINT MUTATION ASSAY OF CI-906 IN CHINESE HAMSTER LUNG CELLS"
		RR 745-00529 AUTHOR: MOYER, C.E. ET AL DATE: 1-OCT-82 "IN VITRO SISTER-CHROMATID EXCHANGE (SCE) ASSAY OF CI-906 IN CHINESE HAMSTER OVARY (CHO) CELLS"

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CONTENT:		
		RR 745-01168 AUTHOR: KROPKO, M.L. ET AL DATE: 14-SEP-87 "IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906 IN V79 CHINESE HAMSTER LUNG CELLS"
		RR 745-01156 AUTHOR: KRISHNA, G. ET AL DATE: 14-SEP-87 "MOUSE MICRONUCLEUS STUDY OF CI-906"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 745-00764 AUTHOR: PARADISO, L.J. ET AL DATE: 5-DEC-84 "ACUTE INTRAVENOUS TOXICITY OF CI-928 IN MALE AND FEMALE B6C3F1 MICE"
		RR 745-00687 AUTHOR: CARMODY, L.P. ET AL DATE: 28-FEB-84 "ACUTE EXPLORATORY INTRAVENOUS TOXICITY OF CI-928 IN MALE AND FEMALE ALBINO RATS"
		RR 745-00747 AUTHOR: PEGG, D.G. ET AL DATE: 27-AUG-84 "EXPLORATORY INTRAVENOUS RISING DOSE STUDY IN BEAGLE DOGS WITH CI-928 (PD 109,548)"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		
		RR 250-01466 AUTHOR: MACALLUM, G.E. ET AL DATE: 5-NOV-86 "EXPLORATORY 2 WEEK DAILY REPEATED DOSE INTRAVENOUS TOXICITY STUDY OF CI-928 (PD 109548) IN RATS"
		RR 250-01476 AUTHOR: MACALLUM, G.E. ET AL DATE: 16-JAN-87 "4 WEEK DAILY REPEATED DOSE INTRAVENOUS TOXICITY STUDY OF CI-928 (PD 109548) IN RATS"
		RR 250-01475 AUTHOR: MACALLUM, G.E. DATE: 16-JAN-87 "EXPLORATORY 2 WEEK INTRAVENOUS TOXICITY STUDY OF CI-928 (PD 109548) IN BEAGLE DOGS"

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RR 250-01483
AUTHOR: MACALLUM, G.E. ET AL
DATE: 23-FEB-87
"4 WEEK REPEATED DOSE INTRAVENOUS TOXICITY STUDY
OF CI-928 (PD 109548) IN BEAGLE DOGS"

RR 745-00986
AUTHOR: NELSON, D.R. ET AL
DATE: 12-DEC-86
"INTRAVENOUS IRRITATION STUDY IN RABBITS WITH
CI-928"

RR 745-00976
AUTHOR: NELSON, D.R. ET AL
DATE: 22-OCT-86
"INTR-ARTERIAL TOLERANCE STUDY IN RABBITS WITH
CI-928"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 745-00633
AUTHOR: KIM, S.N. ET AL
DATE: 18-OCT-83
"STANDARD BACTERIAL MUTAGENICITY PLATE ASSAY OF
CI-928"

RR 745-00892
AUTHOR: PEGG, D.G.
DATE: 12-DEC-85
"ACUTE ORAL TOXICITY STUDY OF PD 109,488 IN
B6C3F1 MICE"

RR 745-00891
AUTHOR: PEGG, D.G. ET AL
DATE: 12-DEC-85
"ACUTE ORAL TOXICITY STUDY OF PD 109,488 IN MALE
AND FEMALE ALBINO RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 745-01220
AUTHOR: DETHLOFF, L.A. ET AL
DATE: 6-MAY-88
"ACUTE INTRAVENOUS TOXICITY STUDY OF PD 109,488 IN
MALE AND FEMALE ALBINO RATS"

RR 745-01221
AUTHOR: DETHLOFF, L.A. ET AL
DATE: 8-APR-88
"ACUTE INTRAVENOUS TOXICITY STUDY OF PD 113,413
AND MALE AND FEMALE ALBINO RATS"

RR 901-00052
AUTHOR: FASSULIOTIS, K. ET AL
DATE: 16-JUN-86

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RR 901-00076
AUTHOR: FASSULIOTIS, K. ET AL
DATE: 16-JUN-86
"ACUTE ORAL TOXICITY (DL50) STUDY OF PD 107438-2
S-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC
ACID HYDROCHLORIDE)) IN RATS FOR OCCUPATIONAL
HEALTH HAZARD EVALUATION"

RR 745-01179
AUTHOR: ANDREWS, L.K. ET AL
DATE: 22-DEC-87
"ACUTE ORAL TOXICITY STUDY OF PD 127,751-2 IN
WISTAR RATS"

RR 720-01435
AUTHOR: BARSOUM, N.J. ET AL
DATE: 21-JAN-86
"ACUTE ORAL TOXICITY STUDY OF CI-939 IN MICE"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 250-01432
AUTHOR: BARDOUM, N.J. ET AL
DATE: 21-JAN-86
"ACUTE ORAL TOXICITY STUDY OF CI-939 IN RATS"

RR 250-01437
AUTHOR: BARSOUM, N.J. ET AL
DATE: 21-JAN-86
"EXPLORATORY ORAL RISING DOSE TOXICITY STUDY OF
CI-939 IN BEAGLE DOGS"

RR 250-01445
AUTHOR: BARSOUM, N.J. ET AL
DATE: 3-APR-86
"EXPLORATORY 4 WEEK DAILY REPEATED DOSE ORAL
TOXICITY STUDY OF CI-939 IN RATS"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 250-01511
AUTHORS: GREAVES, P.
DE LA IGLESIA, F.A.
DATE: 10-NOV-87
"FIFTEEN WEEK ORAL TOXICITY STUDY WITH CI-939
IN RATS"

RR 250-01509
AUTHORS: GREAVES, P.
DE LA IGLESIA, F.A.
DATE: 3-NOV-87
"16 DAY ORAL TOXICITY STUDY OF CI-939 IN BEAGLE
DOGS"

RR 250-01517

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CONTENT:		<p>RR 250-01471 AUTHOR: ROGERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL-HYDROCHLOROTHIAZIDE COMBINATION) IN MICE"</p> <p>RR 250-01484 AUTHOR: ROBERS, S.C. ET AL DATE: 8-JUL-87 "ACUTE ORAL TOXICITY STUDY OF CI-955 (QUINAPRIL-HYDORCHOROTHIAZIDE COMBINATION) IN RATS"</p> <p>RR MEMO-764-00943 AUTHOR: HORVATH, A.M. ET AL DATE: 29-JAN-88 "PLASMA CI-928 AND HYDROCHLOROTHIAZIDE (CI-570) CONCENTRATIONS IN DOGS DURING A EXPLORATORY RISING-DOSE TOXICOLOGY STUDY WITH COMBINATION PRODUCT CI-955 - SHERIDAN PARK TOXICOLOGY STUDY 1353"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 250-01507 AUTHOR: ROGERS, S.C. ET AL DATE: 18-AUG-87 "13 WEEK DAILY REPEATED DOSE ORAL TOXICITY STUDY OF CI-955 IN RATS"</p> <p>RR MEMO-764-00946 AUTHOR: OLSON, S.C. ET AL DATE: 19-JAN-88 "PLASMA CI-928 AND HYDROCHLOROTHIAZIDE (CI-570) CONCENTRATIONS IN RATS DURING 13 WEEKS OF ORAL DOSING WITH THE COMBINATION PRODUCT CI-955 - SHERIDAN PARK TOXICOLOGY STUDY 1363"</p> <p>RR 250-01497 AUTHOR: ROGERS, S.C. ET AL DATE: 9-JUN-87 "EXPLORATORY 2 WEEK TOXICITY STUDY OF CI-955 IN BEAGLE DOGS"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR MEMO-764-00936 AUTHOR: HORVATH, A.M. ET AL DATE: 19-JAN-88 "CI-928 AND HYDROCHLOROTHIAZIDE (CI-570) PLASMA CONCENTRATIONS IN MALE AND FEMALE BEAGLE DOGS FOLLOWING ORAL DOSING WITH THE COMBINATION PRODUCT CI-955 - SHERIDAN PARK TOXICOLOGY STUDY 1362"</p> <p>RR 250-01510 AUTHOR: ROGERS, S.C. ET AL</p>

DATE: 10-SEP-87
"13 WEEK ORAL TOXICITY STUDY OF CI-955 IN BEAGLE
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RR MEMO-764-00944
AUTHOR: OLSON, S.C. ET AL
DATE: 3-FEB-88
"PLASMA CI-928 AND HYDROCHLOROTHIAZIDE (CI-570)
CONCENTRATIONS IN DOGS DURING 13-WEEK ORAL DOSING
WITH THE COMBINATION PRODUCT CI-955 - SHERIDAN
PARK TOXICOLOGY STUDY 1365"

RR MEMO 730-00115
AUTHOR: HUANG, C.C.
DATE: 17-AUG-81
"SYNTHESIS OF CI-906-14C"

RR 740-00271
AUTHOR: PARKER, R.B.
DATE: 13-FEB-79
"METHOD: IN VITRO (BIOCHEMICAL) ASSAY FOR
ANGIOTENSIN CONVERTING ENZYME (ACE) AND THE
INHIBITION OF ACE"

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RR 764-00460
AUTHOR: NORDLOM, G. ET AL
DATE: 29-OCT-85
"DEVELOPMENT OF A RADIOIMMUNOASSAY FOR CI-928,
THE DIACID METABOLITE OF CI-906"

RR MEMO-4192-00302
AUTHOR: ANHUT, H. ET AL
DATE: 28-AUG-87
"CI-928 RADIOIMMUNOASSAY, VALIDATION FOR HUMAN
PLASMA"

RR 764-00441
AUTHOR: TAYLOR, M. ET AL
DATE: 13-FEB-86
"CI-906 AND CI-928: A VALIDATED GAS
CHROMATOGRAPHIC ASSAY FOR HUMAN PLASMA SAMPLES"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-01083
AUTHOR: BURGER, P.J. ET AL
DATE: 24-AUG-88
"A VALIDATED GAS CHROMATOGRAPHIC METHOD TO
DETERMINE CI-906 AND ITS ACTIVE METABOLITE,
CI-928, IN HUMAN URINE"

RR 4192-00292
AUTHORS: HENGY, H.
MOST, M.
DATE: 31-JUL-87
"VALIDATION OF HIGH-PERFORMANCE LIQUID
CHROMATOGRAPHIC ASSAY FOR THE DETERMINATION

OF CI-906 AND CI-928 IN HUMAN PLASMA"

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26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR MEMO-4192-00286

AUTHORS: HENGY, H.

MOST, M.

DATE: 18-MAY-87

"CI-906 AND CI-928 CONCENTRATION IN URINE OBTAINED
FROM THE DIGOXIN/QUINAPRIL-INTERACTIO STUDY (MUN
683/CI-906-209). VALIDATED HPLC-ASSAY FOR
CI-906 AND CI-928 IN URINE"

RR 764-01099

AUTHOR: OLSON, S.C. ET AL

DATE: 31-AUG-88

"COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED
TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE
METABOLITE, QUINAPRILAT (CI-928), IN PRECLINICAL
PHARMACOKINETIC STUDIES"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-01094

AUTHOR: OLSON, S.C. ET AL

DATE: 31-AUG-88

"COMPARISON AND SUMMARY OF ANALYTICAL METHODS
USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS
ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN
CLINICAL PHARMACOKINETIC STUDIES"

RR 764-00188

AUTHOR: BORONDY, P.E. ET AL

DATE: 28-FEB-84

"CI-906-14C: METABOLIC DISPOSITION STUDIES IN
RATS AND MONKEYS, STABILITY TO DEESTERIFICATION
AND ACE INHIBITION IN VITRO"

RR 740-00769

AUTHOR: WONG, A. ET AL

DATE: 13-AUG-81

"BIOPHARMACEUTICAL PROFILE OF CI-906 (CN-109,452)"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00275

AUTHORS: TOOTHAKER, R.D.

MEHTA, S.

DATE: 3-OCT-84

"BIOPHARMACEUTICAL PROFILE OF CI-928"

RR 764-00001

AUTHORS: BORONDY, P.E.

MICHNIEWICZ, B.M.

DATE: 6-JAN-82

"CI-906-14C: PRELIMINARY PHARMACOKINETIC AND
METABOLIC DISPOSITION STUDIES IN LABORATORY
ANIMALS."

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-00652 AUTHOR: FERRY, J.J. ET AL DATE: 12-NOV-86 "BIOAVAILABILITY AND PHARMACOKINETICS OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING SINGLE ORAL AND INTRAVENOUS QUINAPRIL AND CI-928 DOSES ADMINISTERED TO BEAGLE DOGS" RR 4192-00347 AUTHOR: NEUB, M. ET AL DATE: 10-AUG-88 "DOSE PROPORTIONALITY OF QUINAPRIL, QUINAPRILAT (CI-928), AND TWO ADDITIONAL METABOLITES (PD 109488 AND PD 113413) FOLLOWING ORAL QUINAPRIL DOSES OF 25, 50, AND 100 MG/KG IN BEAGLE DOGS. PRECLINICAL PROTOCOL NO. 86045"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-00606 AUTHOR: FERRY, J.J. ET AL DATE: 6-AUG-86 "SINGLE DOSE STUDY TO ASSESS THE POTENTIAL DRUG- DRUG INTERACTION OF QUINAPRIL (CI-906) AND HYCROCHLOROTHIAZIDE (CI-570) IN BEAGLE DOGS" RR 764-00867 AUTHOR: OLSON, S.C. ET AL DATE: 2-OCT-87 "PHARMACOKINETIC DISPOSITION OF 14C-QUINAPRIL AND ITS ACTIVE METABOLITES, CI-928, AFTER SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY VOLUNTEERS, PROTOCOL 906-60"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-01104 AUTHOR: KUGLER, A.R. ET AL DATE: 10-OCT-88 "DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM DIALYSIS METHOD TO DETERMINE QUINAPRIL AND QUINAPRILAT PROTEIN BINDING CHARACTERISTICS" RR 764-00786 AUTHOR: MCNALLY, W. ET AL DATE: 27-APR-87 "WHOLE-BODY AUTORADIOGRAPHIC ANALYSIS OF TISSUE DISTRIBUTION OF 14C-CI-906 IN RATS" RR 764-00268 AUTHORS: JORDAN, R.A. CHANG, T. DATE: 27-AUG-84 "THE EFFECT OF REPEATED ADMINISTRATION OF CI-906 ON THE RAT LIVER MICROSOMAL DRUG METABOLISM"

PARAMETERS"

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CONTENT:

RR MEMO-764-00916
AUTHOR: MICHNIEWICZ, B. ET AL
DATE: 30-NOV-87
"METABOLIC DISPOSITION OF 14C QUINAPRIL IN RATS"

RR MEMO-764-00917
AUTHOR: MICHNIEWICZ, B. ET AL
DATE: 30-NOV-87
"CHARACTERIZATION OF QUINAPRIL METABOLITES IN
URINE OF MAN AND DOG FOLLOWING ADMINISTRATION
OF 14C QUINAPRIL"

RR MEMO-764-01085
AUTHOR: HORVATH, A.M. ET AL
DATE: 26-AUG-88
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE
METABOLITE OF QUINAPRIL HCL, PD 109488, AND THE
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT, PD
113413, IN PATIENTS WITH VARYING DEGREES OF
RENAL FUNCTION - PROTOCOL 906-255"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

ITEM 6: HUMAN PHARMACOKINETICS AND
BIOAVAILABILITY.

RR MEMO-730-00115
AUTHOR: HUANG, C.C.
DATE: 17-AUG-81
"SYNTHESIS OF CI-906-14C"

RR 740-00271
AUTHOR: PARKER, R.B.
DATE: 13-13-FEB-79
"METHODS: IN VITRO (BIOCHEMICAL) ASSAY FOR
ANGIOTENSIN CONVERTING ENZYME (ACE) AND THE
INHIBITION OF ACE"

RR 764-00460
AUTHOR: NORDBLOM, G.
DATE: 29-OCT-85
"DEVELOPMENT OF A RADIOIMMUNOASSAY FOR CI-928, THE
DIACID METABOLITE OF CI-906:

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR MEMO-4192-00302
AUTHOR: ANHUT, H. ET AL
DATE: 28-AUG-87
"CI-928 RADIOIMMUNOASSAY, VALIDATION FOR HUMAN
PLASMA"

RR 4192-00292
AUTHORS: HENGY, H.
MOST, M.
DATE: 31-JUL-87
"VALIDATION OF HIGH-PERFORMANCE LIQUID

CHROMATOGRAPHIC ASSAY FOR THE DETERMINATION OF
CI-906 AND CI-928 IN HUMAN PLASMA"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR MEMO-4192-00286 AUTHORS: HENGY, G. MOST, M. DATE: 18-MAY-87 "CI-906 AND CI-928 CONCENTRATION IN URINE OBTAINED FROM THE DIGOXIN/QUINAPRIL-INTERACTION STUDY (MUN 683/CI-906-209). VALIDATED HPLC-ASSAY FOR CI-906 AND CI-928 IN URINE. RR 764-00441 AUTHOR: TAYLOR, M. ET AL DATE: 13-FEB-86 "CI-906 AND CI-928: A VALIDATED GAS CHROMATOGRAPHIC ASSAY FOR HUMAN PLASMA SAMPLES"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-01083 AUTHOR: BURGER, P.J. ET AL DATE: 24-AUG-88 "A VALIDATED GAS CHROMATOGRAPHIC METHOD TO DETERMINE CI-906 AND ITS ACTIVE METABOLITE, CI-928, IN HUMAN URINE" RR 764-01099 AUTHOR: OLSON, S.C. ET AL DATE: 31-AUG-88 "COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN PRECLINICAL PHARMACOKINETIC STUDIES"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-01094 AUTHOR: OLSON, S.C. ET AL DATE: 31-AUG-88 "COMPARISON AND SUMMARY OF ANALYTICAL METHODS USED TO CHARACTERIZE QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE, QUINAPRILAT (CI-928), IN CLINICAL PHARMACOKINETIC STUDIES" RR 724-00036 AUTHORS: LATTS, J.R. GOULET, J.R. DATE: 23-MAR-84 "A CLINIAL PHARMACOLOGIC STUDY OF CI-906 HCL SOLUTION, PROTOCOL 906-2"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00156 AUTHOR: GRYCZKO, C. ET AL DATE: 30-NOV-83 "ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL ADMINISTRATION OF CI-906 TO NORMAL HUMAN VOLUNTEERS. PROTOCOL 906-2"</p> <p>RR 724-00034 AUTHOR: LATTS, J.R. ET AL DATE: 3-AUG-84 "REPORT OF A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE PHARMACOKINETICS AND TOLERANCE OF CI-906 HCL IN NORMAL HEALTHY SUBJECTS (PROTOCOL 906-5)"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00856 AUTHOR: OLSON, S.C. ET AL DATE: 2-SEP-87 "CLINICAL DOSE PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING 2.5-MG TO 80-MG SINGLE CAPSULE DOSES OF QUINAPRIL, PROTOCOL 906-191"</p> <p>RR 764-00970 AUTHOR: HORVATH, A.M. ET AL DATE: 5-FEB-88 "CLINICAL DOSE-PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING SINGLE 2.5-MG TO 80-MG TABLET DOSES OF QUINAPRIL, PROTOCOL 906-259"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 724-00085 AUTHOR: BERGHOFF, W. ET AL DATE: 8-DEC-88 "REPORT OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED TOLERANCE AND PHARMACOKINETIC STUDY OF SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN NORMAL SUBJECTS (PROTOCOL 906-254-0)"</p> <p>RR 764-01104 AUTHOR: KUGLER, A.R. ET AL DATE: 10-OCT-88 "DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM DIALYSIS METHOD TO DETERMINE QUINAPRIL AND QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"</p>

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-00867 AUTHOR: OLSON, S.C. ET AL DATE: 2-OCT-87 "PHARMACOKINETICS DISPOSITION OF 14C-QUINAPRIL AND ITS ACTIVE METABOLITS, CI-928 AFTER SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY VOLUNTEERS, PROTOCOL 906-60" RR 764-00917 AUTHOR: MICHNIEWICZ, B. ET AL DATE: 30-NOV-87 "CHARACTERIZATION OF QUINAPRIL METABOLITES IN URINE OF MAN AND DOG FOLLOWING ADMINISTRATION OF 14C QUINAPRIL"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 720-02349 AUTHOR: FRANK, G.J. ET AL DATE: 20-NOV-87 "REPORT OF A COMPARATIVE PHARMACOKINETIC STUDY OF ONCE-DAILY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN YOUNG SUBJECTS AND ELDERLY PATIENTS WITH MILD TO MODERATE HYPERTENSION (906-223)" RR 4192-00338 AUTHOR: NEUB, M. ET AL DATE: 24-AUG-88 "PHARMACOKINETICS OF QUINAPRIL (CI-906) AND QUINAPRILAT (CI-928) FOLLOWING SINGLE AND MULTIPLE ORAL DOSES IN YOUNG AND ELDERLY VOLUNTEERS, PROTOCOL 906-222"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 764-01014 AUTHOR: OLSON, S.C. DATE: 8-APR-88 "MULTIPLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN RENAL FAILURE - PROTOCOL 906-AE (906-292)" RR 764-01084 AUTHOR: HORVATH, A.M. ET AL DATE: 25-AUG-88 "THE PHARMACOKIENTICS OF QUINAPRIL HCL AND ITS ACTIVE METABOLITE (QUINAPRILAT) IN PATIENTS WITH VARYING DEGREES OF RENAL FUNCTION - PROTOCOL 906-255"

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26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR MEMO-764-01085
AUTHOR: HORVATH, A.M. ET AL
DATE: 26-AUG-88
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE
METABOLITE OF QUINAPRIL HCL, PD 109488, AND THE
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT,
PD 113413, IN PATIENTS WITH VARYING DEGREES OF
RENAL FUNCTION - PROTOCOL 906-255"

RR 764-00861
AUTHOR: OLSON, S.C. ET AL
DATE: 29-OCT-87
"SINGLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN
PATIENTS WITH HEPATIC IMPAIRMENT SECONDARY TO
ALCOHOL-INDUCED CIRRHOSIS - PROTOCOL 9-032-0"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR MEMO-764-00554
AUTHORS: FERRY, J.
COLBURN, W.
DATE: 30-APR-86
"PHARMACOKINETIC ASSESSMENT OF CI-928 FOLLOWING
MULTIPLE DOSE ADMINISTRATION OF CI-906 TO
PATIENTS WITH MILD TO MODERATE HYPERTENSION.
PROTOCOLS 906: 12-22"

RR MEMO-720-02386
AUTHOR: BERGHOFF, W.
DATE: 18-AUG-88
"REPORT OF A COMPARISON OF QUINAPRIL (CI-906) AND
CI-928 PLASMA CONCENTRATIONS WITH REDUCTION IN
DIASTOLIC BLOOD PRESSURE DURING A 12-WEEK DOUBLE-
BLIND STUDY IN PATIENTS WITH MODERATE TO SEVERE
HYPERTENSION (PROTOCOLS 906-82 THROUGH 906-87,
906-89 THROUGH 906-91, 906-93, 906-95, AND
906-96)"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00779
AUTHOR: FERRY, J.J. ET AL
DATE: 24-APR-87
"SINGLE DOSE PHARMACOKINETIC DRUG-DRUG INTERACTION
STUDY OF QUINAPRIL (CI-906) AND
HYDROCHLOROTHIAZIDE (CI-570) IN HEALTHY
VOLUNTEERS. PROTOCOL 906-211"

RR 764-00820
AUTHOR: HORVATH, A.M. ET AL
DATE: 26-JUN-87
"EFFECT OF MULTIPLE-DOSE PROPRANOLOL
ADMINISTRATION OF SINGLE-DOSE PHARMACOKINETICS
OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928)

IN HEALTHY VOLUNTEERS. PROTOCOL 906-229"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00792 AUTHOR: FERRY, J.J. ET AL DATE: 8-JUN-87 "EFFECT OF QUINAPRIL ON THE MULTIPLE DOSE PHARMACOKINETICS OF DIGOXIN IN HEALTHY VOLUNTEERS, PROTOCOL 906-209"</p> <p>RR 764-00663 AUTHOR: FERRY, J.J. ET AL DATE: 5-JAN-87 "EFFECT OF CIMETIDINE ON SINGLE DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS. PROTOCOL 906-113"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00870 AUTHOR: OLSON, S.C. ET AL DATE: 6-OCT-87 "EFFECT OF QUINAPRIL ON WARFARIN-INDUCED REDUCTION IN PROTHROBIN COMPLEX ACTIVITY IN HEALTHY SUBJECTS - PROTOCOL 906-235"</p> <p>RR 764-00872 AUTHOR: OLSON, S.C. ET AL DATE: 1-OCT-87 "EFFECT OF MAGNESIUM-CONTAINING QUINAPRIL TABLETS ON THE SINGLE-DOSE PHARMACOKINETICS OF TETRACYCLINE IN HEALTHY VOLUNTEERS, PROTOCOL 906-237"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00635 AUTHOR: FERRY, J.J. ET AL DATE: 14-JAN-87 "CLINICAL BIOEQUIVALENCE STUDY COMPARING THREE QUINAPRIL CAPSULES AND A QUINAPRIL ORAL SOLUTION. PROTOCOL 906-99"</p> <p>RR 764-00740 AUTHOR: FERRY, J.J. ET AL DATE: 17-FEB-87 "CLINICAL BIOAVAILABILITY STUDY COMPRING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS, A QUINAPRIL CAPSULE FORMULATION, AND A QUINAPRIL ORAL SOLUTION, PROTOCOL 906-202"</p>

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26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00771
AUTHOR: HORVATH, A.M. ET AL
DATE: 13-APR-87
"CLINICAL BIOAVAILABILITY STUDY COMPARING TWO
PROTOTYPE QUINAPRIL TABLET FORMULATIONS AND A
QUINAPRIL CAPSULE FORMULATION, PROTOCOL 906-234"

RR 764-00887
AUTHOR: HORVATH, A.M. ET AL
DATE: 2-NOV-87
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING
QUINAPRIL 5- AND 40-MG MARKET-IMAGE TABLETS AND
QUINAPRI 20-MG CAPSULES IN HEALTHY VOLUNTEERS -
PROTOCOL 906-230"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00808
AUTHOR: FERRY, J.J. ET AL
DATE: 26-JUN-87
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING
QUINAPRIL 2.5-MG MARKET-IMAGE TABLETS AND
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS,
PROTOCOL 906-239"

RR 764-00556
AUTHOR: FERRY, J. ET AL
DATE: 11-JUN-86
"EFFECT OF FOOD ON CI-906 (QUINAPRIL) AND CI-928
PHARMACOKINETICS FOLLOWING ORAL DOSING OF CI-906
TO HEALTHY SUBJECTS. PROTOCOL 906-80"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

ITEM 8: CLINICAL DATA

RR 724-00036
AUTHORS: LATTS, J.R.
GOULET, J.R.
DATE: 23-MAR-84
"A CLINICAL PHARMACOLOGIC STUDY OF CI-906 HCL
SOLUTION, PROTOCOL 906-2"

RR MEMO-764-00156
AUTHOR: GRZYCKO, C. ET AL
DATE: 30-NOV-83
"ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL
ADMINISTRATION OF CI-906 TO NORMAL HUMAN
VOLUNTEERS. PROTOCOL 906-2"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR MEMO-764-00131 AUTHORS: BORONDY, P.E. EASTON, M.E. DATE: 6-JUN-83 "INHIBITION OF PLASMA ANGIOTENSIN CONVERTING ENZYME (ACE) ACTIVITY FOLLOWING PERORAL ADMINISTRATION OF CI-906 TO NORMAL HUMAN VOLUNTEERS. PROTOCOL CI-906-2"</p> <p>RR 724-00034 AUTHOR: LATTS, J.R. ET AL DATE: 3-AUG-84 "REPORT OF A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE PHARMACOKINETICS AND TOLERANCE OF CI-906 HCL IN NORMAL HEALTHY SUBJECTS (PROTOCOL 906-5)"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00856 AUTHOR: OLSON, S.C. ET AL DATE: 2-SEP-87 "CLINICAL DOSE PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING 2.5-MG TO 80-MG SINGLE CAPSULE DOSE OF QUINAPRIL, PROTOCOL 906-191"</p> <p>RR 764-00970 AUTHOR: HORVATH, A.M. ET AL DATE: 5-FEB-88 "CLINICAL DOSE-PROPORTIONALITY STUDY OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) FOLLOWING SINGLE 2.5-MG TO 80-MG TABLET DOSES OF QUINAPRIL, PROTOCOL 906-259"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR MEMO-764-01061 AUTHORS: OLSON, S.C. COLBURN, W.A. DATE: 20-JUL-88 "A PRELIMINARY ESTIMATE OF THE EFFECTIVE ACCUMULATION HALF-LIFE FOR QUINAPRILAT"</p> <p>RR 724-00085 AUTHOR: BERGHOFF, W. ET AL DATE: 8-DEC-88 "REPORT OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED TOLERANCE AND PHARMACOKINETIC STUDY OF SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN NORMAL SUBJECTS (PROTOCOL 906-254-0)"</p>

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-01104 AUTHOR: KUGLER, A.R. ET AL DATE: 10-OCT-88 "DEVELOPMENT AND APPLICATION OF AN EQUILIBRIUM DIALYSIS METHOD TO DETERMINE QUINAPRIL AND QUINAPRILAT PROTEIN BINDING CHARACTERISTICS"</p> <p>RR 764-00867 AUTHOR: OLSON, S.C. ET AL DATE: 2-OCT-87 "PHARMACOKINETIC DISPOSITION OF ¹⁴C-QUINAPRIL AND ITS ACTIVE METABOLITE, CI-928, AFTER SINGLE AND MULTIPLE ORAL DOSES OF QUINAPRIL TO HEALTHY VOLUNTEERS, PROTOCOL 906-60"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR MEMO-764-00917 AUTHOR: MICHNIEWICZ, B. ET AL DATE: 30-NOV-87 "CHARACTERIZATION OF QUINAPRIL METABOLITES IN URINE OF MAN AND DOG FOLLOWING ADMINISTRATION OF ¹⁴C QUINAPRIL"</p> <p>RR 720-02349 AUTHOR: FRANK, G.J. ET AL DATE: 20-NOV-87 "REPORT OF A COMPARATIVE PHARMACOKINETICS STUDY OF ONCE-DAILY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN YOUNG SUBJECTS AND ELDERLY PATIENTS WITH MILD TO MODERATE HYPERTENSION (906-223)"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 4192-00338 AUTHOR: NEUB, M. ET AL DATE: 24-AUG-88 "PHARMACOKINETICS OF QUINAPRIL (CI-906) AND QUINAPRILAT (CI-928) FOLLOWING SINGLE AND MULTIPLE ORAL DOSES IN YOUNG AND ELDERLY VOLUNTEERS, PROTOCOL 906-222"</p> <p>RR 764-01014 AUTHOR: OLSON, S.C. ET AL DATE: 8-APR-88 "MULTIPLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL (CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN RENAL FAILURE - PROTOCOL 906-AE (906-292)"</p>

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26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-01084
AUTHOR: HORVATH, A.M. ET AL
DATE: 25-AUG-88
"THE PHARMACOKINETICS OF QUINAPRIL HCL AND ITS
ACTIVE METABOLITE (QUINAPRILAT) IN PATIENTS WITH
VARYING DEGREES OF RENAL FUNCTION - PROTOCOL
906-255"

RR MEMO-764-01085
AUTHOR: HORVATH, A.M. ET AL
DATE: 260-AUG-88
"THE PHARMACOKINETICS OF THE DIKETOPIPERAZINE
METABOLITE OF QUINAPRIL HCL, PD 109488, AND
DIKETOPIPERAZINE METABOLITE OF QUINAPRILAT,
PD 113413, IN PATIENTS WITH VARYING DEGREES OF
RENAL FUNCTION - PROTOCOL 906-255"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00861
AUTHOR: OLSON, S.C. ET AL
DATE: 29-OCT-87
"SINGLE ORAL DOSE PHARMACOKINETICS OF QUINAPRIL
(CI-906) AND ITS ACTIVE METABOLITE (CI-928) IN
PATIENTS WITH HEPATIC IMPAIRMENT SECONDARY TO
ALCOHOL-INDUCED CIRRHOSIS - PROTOCOL 9-032-0"

RR 764-00779
AUTHOR: FERRY, J.J. ET AL
DATE: 24-APR-87
"SINGLE DOSE PHARMACOKINETIC DRUG-DRUG
INTERACTION STUDY OF QUINAPRIL (CI-906) AND
HYDROCHLOROTHIAZIDE (CI-570) IN HEALTHY
VOLUNTEERS. PROTOCOL 906-211"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00820
AUTHOR: HORVATH, A.M. ET AL
DATE: 26-JUN-87
"EFFECT OF MULTIPLE-DOSE PROPRANOLOL
ADMINISTRATION OF SINGLE-DOSE PHARMACOKINETICS
OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928)
IN HEALTHY VOLUNTEERS. PROTOCOL 906-229"

RR 764-00792
AUTHOR: FERRY, J.J. ET AL
DATE: 8-JUN-87
"EFFECT OF QUINAPRIL ON THE MULTIPLE DOSE
PHARMACOKINETICS OF DIGOXIN IN HEALTHY
VOLUNTEERS, PROTOCOL 906-209"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00663 AUTHOR: FERRY, J.J. ET AL DATE: 5-JAN-87 "EFFECT OF CIMETIDINE ON SINGLE DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (CI-928) IN HEALTHY VOLUNTEERS. PROTOCOL 906-113"</p> <p>RR 764-00870 AUTHOR: OLSON, S.C. ET AL DATE: 6-OCT-87 "EFFECT OF QUINAPRIL ON WARFARIN-INDUCED REDUCTION IN PROTHROMBIN COMPLEX ACTIVITY IN HEALTHY SUBJECTS - PROTOCOL 906-235"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00872 AUTHOR: OLSON, S.C. ET AL DATE: 1-OCT-87 "EFFECT OF MAGNESIUM-CONTAINING QUINAPRIL TABLETS ON THE SINGLE-DOSE PHARMACOKINETICS OF TETRACYCLINE IN HEALTHY VOLUNTEERS, PROTOCOL 906-237"</p> <p>RR 764-00635 AUTHOR: FERRY, J.J. ET AL DATE: 14-JAN-87 "CLINICAL BIOEQUIVALENCE STUDY COMPARING THREE QUINAPRIL CAPSULES AND A QUINAPRIL ORAL SOLUTION. PROTOCOL 906-99"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 764-00740 AUTHOR: FERRY, J.J. ET AL DATE: 17-FEB-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS, A QUINAPRI CAPSULE FORMULATION, AND A QUINAPRIL ORAL SOLUTION, PROTOCOL 906-202"</p> <p>RR 764-00771 AUTHOR: HORVATH, A.M. ET AL DATE: 13-APR-87 "CLINICAL BIOAVAILABILITY STUDY COMPARING TWO PROTOTYPE QUINAPRIL TABLET FORMULATIONS AND A QUINAPRIL CAPSULE FORMULATION, PROTOCOL 906-234"</p>

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26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00887
AUTHOR: HORVATH, A.M. ET AL
DATE: 2-NOV-87
"SINGLE-DOSE BIOEQUIVALNCE STUDY COMPARING
QUINAPRIL 5- AND 40-MG MARKET-IMAGE TABLETS AND
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS -
PROTOCOL 906-230"

RR 764-00808
AUTHOR: FERRY, J.J. ET AL
DATE: 26-JUN-87
"SINGLE-DOSE BIOEQUIVALENCE STUDY COMPARING
QUINAPRIL 2.5-MG MARKET-IMAGE TABLETS AND
QUINAPRIL 20-MG CAPSULES IN HEALTHY VOLUNTEERS,
PROTOCOL 906-239"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 764-00556
AUTHOR: FERRY, J. ET AL
DATE: 11-JUN-86
"EFFECT OF FOOD ON CI-906 (QUINAPRIL) IND CI-928
PHARMACOKINETICS FOLLOWING ORALD DOSING OF CI-906
TO HEALTHY SUBJECTS. PROTOCOL 906-80"

RR 724-00028
AUTHOR: PEARSE, S.B.
DATE: 18-FEB-83
"A STUDY OF THE EFFECTS OF CI-906, IN INHIBITOR OF
ANGIOTENSIN CONVERTING ENZYME, ON THE RENIN-
ANGIOTENSIN-ALDOSTERONE SYSTEM AND RELATED
CARDIOVASCULAR RESPONSES AFTER ANGIOTENSIN-1
CHALLENGE. PART 1: DOSE-RANGING STUDY IN TWO
HEALTHY MEN. PART 2: DURATION OF ACTION STUDY
IN FIVE HEALTHY MEN. {PROTOCOL 906-1 (P.197)}

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR MEMO-764-00303
AUTHOR: GRYCZKO, C. ET AL
DATE: 18-DEC-84
"ACE INHIBITOR LEVELS IN PLASMA FOLLOWING PERORAL
ADMINISTRATION OF CI-906 TO NORMAL HUMAN
VOLUNTEERS AFTER ANGIOTENSIN-1 CHALLENGE.
PROTOCOL 906-1"

RR 724-00039
AUTHORS: GOULET, J.R.
LATTS, J.R.
DATE: 24-OCT-84
"REPORT OF A STUDY TO DETERMINE THE EFFECTIVE DOSE
AND SAFETY OF CI-906 HCL IN PATIENTS WITH MILD
TO MODERATE UNCOMPLICATED HYPERTENSION (PROTOCOL
906-4)"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 724-00041 AUTHORS: LATTS, J.R. GOULET, J.R. DATE: 10-JAN-85 "REPORT OF A STUDY TO DETERMINE THE SAFETY AND MINIMUM ANTIHYPERTENSIVE DOSE OF CI-906 HCL (PROTOCOL 906-3)" RR 724-00051 AUTHOR: GOULET, J.R. ET AL DATE: 21-MAR-85 "REPORT OF PROTOCOLS 906-6 AND -8: A 28-DAY DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY OF QUINAPRIL HYDROCHLORIDE (CI-906) IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION; AND PROTOCOL 906-10, A LONG-TERM EXTENSION OF PROTOCOL 906-6"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR MEMO-764-00293 AUTHORS: TOOTHAKER, R.D. MEHTA, S. DATE: 9-JAN-85 "ACE INHIBITOR LEVELS IN SERUM FOLLOWING MULTIPLE PERORAL DOSES OF CI-906 TO HYPERTENSIVE PATIENTS. PROTOCOL 906-6" RR MEMO-764-00312 AUTHORS: TOOTHAKER, R.D. MEHTA, S. DATE: 26-DEC-84 "ACE INHIBITOR LEVELS IN SERUM FOLLOWING MULTIPLE PERORAL DOSES OF CI-906 TO HYPERTENSIVE PATIENTS. PROTOCOL 906-8"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 724-00093 AUTHOR: BECKER, M. ET AL DATE: 1-OCT-88 "REPORT OF A PLACEBO-CONTROLLED 24-HOUR BLOOD PRESSURE MONITORING STUDY OF ONCE AND TWICE DAILY ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-250-1 THROUGH 906-250-3)" RR MEMO-720-02325 AUTHOR: FRNAK, G.J. ET AL DATE: 22-MAY-87 "TWENTY-FOUR HOUR BLOOD PRESSURE AND HEART RATE RESPONSES TO ONCE-DAILY QUINAPRIL HYDROCHLORIDE (CI-906) MEASURED BY AMBULATORY MONITORING IN HYPERTENSIVE PATIENTS RECEIVING OPEN-LABEL

QUINAPRIL (PROTOCOLS 906-33 AND 906-15)"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 720-02331 AUTHOR: IMBARRATO, C. ET AL DATE: 15-MAY-87 "EFFECTS OF ORAL QUINAPRIL ON BLOOD PRESSURE, HEART RATE, AND PULMONARY FUNCTION MEASUREMENTS IN HEALTHY SUBJECTS (PROTOCOL 9066-232-0)" RR 4301-00030 AUTHORS: FRIEDRICH. T. SAUERMANN, W. DATE: 31-AUG-87 "REPORT OF A DOUBLE-BLIND, FIXED-DOSE, PLACEBO- CONTROLLED, 2-WEEK STUDY OF THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION UNDER EXERCISE STRESS TEST CONDITIONS"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR X-724-00072 AUTHOR: FRANK. G.J. ET AL DATE: 17-JUL-87 "REPORT OF A SINGLE RISING-DOSE STUDY AND MULTIPLE-DOSE EXTENDED-TREATMENT STUDY CONDUCTED TO ASSESS THE SAFETY, PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF QUINAPRIL (CI-906) CAPSULES ADMINISTERED TO PATIENTS WITH CONGESTIVE HEART FAILURE (PROTOCOLS 906-7 AND 906-9)" RR 724-00082 AUTHOR: FRANK, G.J. ET AL DATE: 19-NOV-87 "A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY AND PHARMACOLOGICAL ACTIVITY OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH CONGESTIVE HEART FAILURE {PROTOCOL 906-50 (P.239)}"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 724-00079 AUTHOR: FRANK, G.J. ET AL DATE: 6-NOV-87 "A SINGLE, RISING-DOSE TRIAL TO ASSESS THE SAFETY, PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH CONGESTIVE HEART FAILURE {PROTOCOL 906-61 (P.254)}" RR 724-00083 AUTHOR: FRANK, G.J. ET AL DATE: 19-DEC-87 "A 16-WEEK MULTIPLE-DOSE STUDY OF THE SAFETY

PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS
OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH
CONGESTIVE HEART FAILURE {PROTOCOL 906-51
(P.240)}"

CI NUMBER= 906 APPL NUMBER= 19-885

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 724-00081 AUTHOR: FRANK, G.J. ET AL DATE: 30-NOV-87 "A 16-WEEK, MULTIPLE-DOSE STUDY OF THE SAFETY, PHARMACOLOGICAL ACTIVITY, AND PHARMACOKINETICS OF ORALLY ADMINISTERED QUINAPRIL IN PATIENTS WITH CONGESTIVE HEART FAILURE {PROTOCOL 906-62 (P.255)}" RR X-720-02147 AUTHOR: FRANK, G.J. ET AL DATE: 10-AUG-88 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED, SIX-WEEK, PARALLEL-GROUP, DOSE- RESPONSE STUDY COMPARING EFFICACY AND SAFETY OF PLACEBO AND 5, 10, AND 20 MG TO PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-12 TO 906-22)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR X-720-02185 AUTHOR: BOVENKERK, W.E. ET AL DATE: 26-AUG-88 "REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK, PARALLEL-GROUP STUDY COMPARING THE EFFICACY AND SAFETY OF ONCE-A-DAY, ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH PLACEBO; AND ALSO COMPARING QUINAPRIL MONOTHERAPY WITH CHLORTHALIDONE AND WITH CONCOMITANT QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-30 THROUGH 906-38, 906-40 THROUGH 906-46)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR X-720-02394 AUTHOR: BERMAN, S.J. ET AL DATE: 19-NOV-88 "AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOSE-RESPONSE, MULTICENTER STUDY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-238-1 TO 5, 906-235-7 TO 16, AND 906-238-18 TO 26" RR C-720-02327 AUTHOR: FRANK, G.J. ET AL DATE: 24-AUG-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED, 12-WEEKS STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-DAILY (BID) AND ONCE-DAILY (QD) DOSES OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-12, 906-18, 906-20, 906-22, 906-24, 906-26, 906-28, 906-30, 906-32, 906-34, 906-36, 906-38, 906-40, 906-42, 906-44, 906-46, 906-48, 906-50, 906-52, 906-54, 906-56, 906-58, 906-60, 906-62, 906-64, 906-66, 906-68, 906-70, 906-72, 906-74, 906-76, 906-78, 906-80, 906-82, 906-84, 906-86, 906-88, 906-90, 906-92, 906-94, 906-96, 906-98, 906-100, 906-102, 906-104, 906-106, 906-108, 906-110, 906-112, 906-114, 906-116, 906-118, 906-120, 906-122, 906-124, 906-126, 906-128, 906-130, 906-132, 906-134, 906-136, 906-138, 906-140, 906-142, 906-144, 906-146, 906-148, 906-150, 906-152, 906-154, 906-156, 906-158, 906-160, 906-162, 906-164, 906-166, 906-168, 906-170, 906-172, 906-174, 906-176, 906-178, 906-180, 906-182, 906-184, 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906-408, 906-410, 906-412, 906-414, 906-416, 906-418, 906-420, 906-422, 906-424, 906-426, 906-428, 906-430, 906-432, 906-434, 906-436, 906-438, 906-440, 906-442, 906-444, 906-446, 906-448, 906-450, 906-452, 906-454, 906-456, 906-458, 906-460, 906-462, 906-464, 906-466, 906-468, 906-470, 906-472, 906-474, 906-476, 906-478, 906-480, 906-482, 906-484, 906-486, 906-488, 906-490, 906-492, 906-494, 906-496, 906-498, 906-500, 906-502, 906-504, 906-506, 906-508, 906-510, 906-512, 906-514, 906-516, 906-518, 906-520, 906-522, 906-524, 906-526, 906-528, 906-530, 906-532, 906-534, 906-536, 906-538, 906-540, 906-542, 906-544, 906-546, 906-548, 906-550, 906-552, 906-554, 906-556, 906-558, 906-560, 906-562, 906-564, 906-566, 906-568, 906-570, 906-572, 906-574, 906-576, 906-578, 906-580, 906-582, 906-584, 906-586, 906-588, 906-590, 906-592, 906-594, 906-596, 906-598, 906-600, 906-602, 906-604, 906-606, 906-608, 906-610, 906-612, 906-614, 906-616, 906-618, 906-620, 906-622, 906-624, 906-626, 906-628, 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906-852, 906-854, 906-856, 906-858, 906-860, 906-862, 906-864, 906-866, 906-868, 906-870, 906-872, 906-874, 906-876, 906-878, 906-880, 906-882, 906-884, 906-886, 906-888, 906-890, 906-892, 906-894, 906-896, 906-898, 906-900, 906-902, 906-904, 906-906, 906-908, 906-910, 906-912, 906-914, 906-916, 906-918, 906-920, 906-922, 906-924, 906-926, 906-928, 906-930, 906-932, 906-934, 906-936, 906-938, 906-940, 906-942, 906-944, 906-946, 906-948, 906-950, 906-952, 906-954, 906-956, 906-958, 906-960, 906-962, 906-964, 906-966, 906-968, 906-970, 906-972, 906-974, 906-976, 906-978, 906-980, 906-982, 906-984, 906-986, 906-988, 906-990, 906-992, 906-994, 906-996, 906-998, 906-1000, 906-1002, 906-1004, 906-1006, 906-1008, 906-1010, 906-1012, 906-1014, 906-1016, 906-1018, 906-1020, 906-1022, 906-1024, 906-1026, 906-1028, 906-1030, 906-1032, 906-1034, 906-1036, 906-1038, 906-1040, 906-1042, 906-1044, 906-1046, 906-1048, 906-1050, 906-1052, 906-1054, 906-1056, 906-1058, 906-1060, 906-1062, 906-1064, 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AND 906-52 TO 906-59) "

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26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR X-720-02346

AUTHOR: EVANS, R. ET AL

DATE: 26-AUG-88

"A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED,
12-WEEK STUDY TO COMPARE THE EFFICACY AND SAFETY
OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE
(CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN
PATIENTS WITH MILD TO MODERATE ESSENTIAL
HYPERTENSION (PROTOCOL 906-114 TO 906-131,
906-133, 906-134, 906-136 TO 906-138)"

RR 720-02338

AUTHOR: FRANK, G.J. ET AL

DATE: 10-DEC-87

"A MULTICENTER, 28-WEEK, PARALLEL GROUP,
RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING STUDY OF
QUINAPRIL (CI-906) VERSUS ENALAPRIL IN THE
TREATMENT OF MILD TO MODERATE ESSENTIAL
HYPERTENSION (PROTOCOL WLI-9-003-4)"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 4301-00023

AUTHORS: WOELFING, A.

LILIETHAL, J.

DATE: 11-SEP-87

"REPORT OF A MULTICENTER, DOUBLE-BLIND, 28-WEEK
STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-
A-DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE
WITH ENALAPRIL IN PATIENTS WITH MILD TO MODERATE
HYPERTENSION (CT 890-200)"

RR 720-02332

AUTHOR: FRANK, G.J. ET AL

DATE: 22-DEC-87

"OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND,
12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY
OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH
CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE
HYPERTENSION (PROTOCOLS 906-82 TO 87, -89 TO 91,
-93, -95, -96)"

26-JAN-89 1 INITIAL NDA - CONTINUED
CONTENT:

RR 4301-00025

AUTHORS: WOELFING, A.

STERN, K.

DATE: 21-SEP-88

"REPORT OF A MULTICENTER, DOUBLE-BLIND, PARALLEL
28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY
OF TWICE A DAY ORALLY ADMINISTERED QUINAPRIL
HYDROCHLORIDE WITH TWICE A DAY ORALLY
ADMINISTERED ENALAPRIL WHEN BOTH GIVEN IN ADDITION
TO ONCE A DAY CHLORTHALIDONE IN PATIENTS WITH
MODERATE TO SEVERE HYPERTENSION (CT 890-170)"

RR 720-02337

AUTHOR: FRANK, G J. ET AL

DATE: 6-NOV-87

"A 28-WEEK PARALLEL GROUP DOUBLE-BLIND DOSE-
RANGING STUDY OF QUINAPRIL (CI-906) IN THE
TREATMENT OF MILD TO MODERATE ESSENTIAL
HYPERTENSION (PROTOCOL 9-007)"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 720-02388 AUTHOR: BECKER, M. ET AL DATE: 8-SEP-88 "REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, FIXED-DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-12, 906-13, AND 906-15 TO 906-22)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 720-02334 AUTHOR: FRANK, G.J. ET AL DATE: 25-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, PLACEBO-CONTROLLED STUDY TO DETERMINE THE COMPARATIVE EFFICACY AND SAFETY OF ORALLY-ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906), CHLORTHALIDONE, AND QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION. (RR-X 720-02185) (PROTOCOLS 906-30 TO 38, -41 TO 46)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR X-720-02318 AUTHOR: FRANK, G.J. ET AL DATE: 19-NOV-87 "INTERIM REPORT OF THE OPEN-LABLE PHASE OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 906-86, 906-89 TO 906-91, 906-93, 906-95, 906-96)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 720-02369 AUTHOR: FRANK, G.J. ET AL DATE: 24-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-114 TO 906-131, 906-133, 906-134, 906-137, 906-138)"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR X-720-02392 AUTHOR: EVANS, R. ET AL DATE: 11-NOV-88 "INTERIM SUMMARY REPORT OF THE OPEN-LABEL PHASE OF FOUR MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDIES TO DETERMINE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH ESSENTIAL HYPERTENSION (PROTOCOLS 906-12, 906-13, 906-15 TO 906-22, 906-30 TO 906-38, 906-41 TO 906-46, 906-82 TO 906-86, 906-89 TO 906-91, 906-93, 906-95, 906-96, 906-114 TO 906-124, 906-126 TO 906-131, 906-133, 906-134, 906-137 AND 906-138)"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR X-720-02345 AUTHOR: FRANK, G.J. ET AL DATE: 25-NOV-87 "INTERIM REPORT OF THE OPEN-LABEL PHASE OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF TWICE- DAILY (BID) AND ONCE-DAILY (QD) ORAL DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-11, 906-48, 906-49, AND 906-52 TO 906-59)"</p> <p>RR 764-00523 AUTHOR: FERRY, J. ET AL DATE: 16-MAY-86 "CLINICAL BIOPHARMACEUTICAL STUDY OF TWO NEW PROTOTYPE FORMULATION CAPSULES OF QUINAPRIL (CI-906) AND AN IMMEDIATE-RELEASE CAPSULE. PROTOCOL 906-81"</p>
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		<p>RR 4301-00015 AUTHOR: BAKOVIC-ALT, R. ET AL DATE: 18-AUG-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO CONTROLLED, 12-WEEK STUDY DETERMINING THE EFFICACY AND SAFETY OF TWICE-A-DAY, ORALLY ADMINISTERED QUINAPRIL 5 MG, 10 MG AND 20 MG IN THE TREATMENT OF CONGESTIVE HEART FAILURE (CT 891-140)"</p> <p>RR MEMO-4301-00032 AUTHOR: BAKOVIC-ALT, R. ET AL DATE: 11-SEP-87 "REPORT OF A ONE-YEAR OPEN-LABEL MULTICENTER STUDY FOLLOWING A 12-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO DETERMINE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH</p>

CONGESTIVE HEART FAILURE (INTERIM ANALYSIS,
CT 891-140 FF)"

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26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		ITEM 10: STATISTICAL SECTION RR X-720-02147 AUTHOR: FRANK, G.J. ET AL DATE: 10-AUG-88 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, SIX-WEEK, PARALLEL-GROUP, DOSE-RESPONSE STUDY COMPARING EFFICACY AND SAFETY OF PLACEBO AND 5, 10, AND 20 MG QUINAPRIL HYDROCHLORIDE (CI-906) ADMINISTERED ORALLY ONCE A DAY TO PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-12 TO 906-22)"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		RR X-720-02185 AUTHOR: BOVENKERK, W.E. DATE: 26-AUG-88 "REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK, PARALLEL-GROUP STUDY COMPARING THE EFFICACY AND SAFETY OF ONCE-A-DAY, ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) WITH PLACEBO; AND ALSO COMPARING QUINAPRIL MONOTHERAPY WITH CHLORTHALIDONE AND WITH CONCOMITANT QUINAPRIL PLUS CHLORTHALIDONE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-30 THROUGH 906-38, 906-40 THROUGH 906-46)"
26-JAN-89	1	INITIAL NDA - CONTINUED
CONTENT:		RR X-720-02394 AUTHOR: BERMAN, S.J. ET AL DATE: 18-NOV-88 "AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOSE-RESPONSE, MULTICENTER STUDY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (PROTOCOLS 906-238-1 TO 5, 906-238-7 TO 16, 906-238-18 TO 26)" RR X-720-02327 AUTHOR: FRANK, G.J. ET AL DATE: 24-AUG-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE-DAILY (BID) AND ONCE-DAILY (QD) DOSES OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) IN PATIENTS WITH HYPERTENSION (PROTOCOLS 906-11, 906-48, 906-49, AND 906-52 TO 906-59)"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR X-720-02346 AUTHOR: EVANS, R. ET AL DATE: 26-AUG-88 "A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE (CI-906) TO ORALLY ADMINISTERED CAPTOPRIL IN PATIENTS WITH MILD TO MODERATE ESSENTIAL HYPERTENSION (PROTOCOL 906-114 TO 906-131, 906-133, 906-134, 906-136 TO 906-138)" RR 720-02338 AUTHOR: FRANK, G.J. ET AL DATE: 10-DEC-87 "A MULTICENTER, 28-WEEK, PARALLEL GROUP, RANDOMIZED, DOUBLE-BLIND, DOSE-REANDING STUDY OF QUINAPRIL (CI-906) VERSUS ENALAPRIL IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION (PTOTOCOL WLI-9-003-4)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 4301-00023 AUTHORS: WOELFING, A. LILIENTHAL, J. DATE: 11-SEP-87 "REPORT OF A MULTICENTER, DOUBLE-BLIND, 28-WEEK STUDY COMPARING THE EFFICACY AND SAFEY OF TWICE- A-DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH ENALAPRIL IN PATIENTS WITH MILD TO MODERATE HYPERTENSION (CT 890-200)" RR 720-02332 AUTHOR: FRANK, G.J. ET AL DATE: 22-DEC-87 "OVERALL REPORT OF A MULTICENTER, DOUBLE-BLIND, 12-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH CAPTOPRIL IN THE TREATMENT OF MODERATE TO SEVERE HYPERTENSION (PROTOCOLS 906-82 TO 87, -89 TO 91, -93, -95, -96)"
26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED RR 4301-00025 AUTHORS: WOELFING, A. STERN, K. DATE: 21-SEP-88 "REPORT OF A MULTICENTER, DOUBLE-BLIND, PARALLEL 28-WEEK STUDY COMPARING THE EFFICACY AND SAFETY OF TWICE A DAY ORALLY ADMINISTERED QUINAPRIL HYDROCHLORIDE WITH TWICE A DAY ORALLY ADMINISTERED ENALPRIL WHEN BOTH GIVEN IN ADDITION TO ONCE A DAY CHLORTHALIDONE IN PATIENTS WITH MODERATE TO SEVERE HYPERTENSION (CT 800-170)"

RR 720-02337

AUTHOR: FRANK, G.J. ET AL

DATE: 6-NOV-87

"A 28-WEEK PARALLEL GROUP DOUBLE-BLIND DOSE-
RANGING STUDY OF QUINAPRIL (CI-906) IN THE
TREATMENT OF MILD TO MODERATE ESSENTIAL
HYPERTENSION (PROTOCOL 9-007)"

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26-JAN-89 CONTENT:	1	INITIAL NDA - CONTINUED ITEM 11: CASE REPORT TABULATIONS ITEM 12: CASE REPORT FORMS ITEM 13: PATENT AND MARKET EXCLUSIVITY INFORMATION.
01-FEB-89 CONTENT:		LETTER FROM FDA ACKNOWLEDGING RECEIPT (NDA 19-885) LETTER FROM: MORGENSTERN, NATALIA A. RE: ACKNOWLEDGEMENT OF RECEIPT OF NDA ON 26-JAN-89; NUMBER 19-885 ASSIGNED.
10-MAY-89 CONTENT:		FDA CONTACT MEMO MEMO RE: DRUG EVALUATION CONTACT PERSON: CUNNINGHAM, DONNA TELEPHONE CONVERSATION RE: THE SUBMISSION OF SAMPLES FOR BOTH DRUG SUBSTANCE AND DRUG PRODUCT ANALYTIC METHODS TO DETROIT AND ST. LOUIS.
11-MAY-89 CONTENT:		FDA CONTACT MEMO MEMO RE: HPLC AND PACKAGING. CONTACT PERSON: CUNNINGHAM, DONNA TELEPHONE CONVERSATION RE: THE HPLC ANALYTIC METHOD FOR DIASTERIOMERIC IMPURITIES IMPROVEMENT AND TO DISCUSS INCORPORATING THE IMPROVED METHOD INTO THE PACKAGES.
18-MAY-89 CONTENT:		EXPORT APPLICATION DRUG TO: FRANCE
23-MAY-89 CONTENT:		LETTER RE: METHOD VALIDATION LETTER TO: SCHNEIDER, LEWIS F. (DETROIT, MI) DREW, HENRY (ST. LOUIS, MO) RE: METHOD VALIDATION SAMPLES.
23-MAY-89 CONTENT:	2	MINUTES OF FDA MEETING DATE: 17-MAY-89 FDA MEETING TO DISCUSS THIS NDA AND THE FOLLOWING: 1) COPY OF THE STUDY REPORTS. 2) LETTER SENT TO DR. BASIL FRIEDMAN.

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25-MAY-89 LETTER FROM FDA RE: EXPORT APPLICATION
CONTENT:

LETTER FROM: COOPER, MARY F.
RE: REQUEST ADDITIONAL INFORMATION REGARDING THE
EXPORT APPLICATION TO FRANCE.
CROSS REFERENCE: DATE - 18-MAY-89

26-MAY-89 SAFETY UPDATE
CONTENT:

VOLUMES=77
ITEM 1: SUBMISSION INDEX.
ITEM 5: NONCLINICAL PHARMACOLOGY AND TOXICOLOGY.

RR 745-01450
AUTHOR: GOUGH, A.W. ET AL
DATE: 8-MAY-89
"HISTOPATHOLOGIC REVIEW OF KIDNEYS FROM RODENT
CHRONIC TOXICITY STUDIES AND TUMOR BIOASSAYS
WITH CI-906"

RR 745-01384
AUTHOR: MACDONALD, J.R. ET AL
DATE: 9-MAY-89
"EFFECTS OF CI-906 ADMINISTERED ORALLY FOR FOUR
WEEKS ON RENAL FUNCTIONAL PARAMETERS IN MALE
RATS"

26-MAY-89 SAFETY UPDATE - CONTINUED
CONTENT:

RR 745-01350
AUTHOR: DETHLOFF, L.A. ET AL
DATE: 10-MAY-89
"THE EFFECTS OF CI-906 (QUINAPRIL) ON RENAL
FUNCTION AND RENAL HEMODYNAMICS IN RATS"

RR 745-01430
AUTHOR: SUSICK, R.L. ET AL
DATE: 9-MAY-89
"RENAL FUNCTION AND HEMODYNAMICS IN DOGS AFTER
THIRTEEN-WEEK ORAL ADMINISTRATION OF CI-906"

RR 745-01408
AUTHOR: HENEK, J.W.
DATE: 12-MAY-89
"TWO-WEEK ORAL TOXICITY STUDY OF CI-906 IN FEMALE
RABBITS"

26-MAY-89 SAFETY UPDATE - CONTINUED
CONTENT:

RR 745-01412
AUTHOR: PETRERE, J.A. ET AL
DATE: 9-MAY-89
"MODIFIED PERINATAL-POSTNATAL STUDY IN RATS WITH
CI-906"

RR 745-01421

AUTHOR: GOUGH, A.W. ET AL
DATE: 9-MAY-89
"IN VITRO CHROMOSOMAL ABERRATION ASSAY OF CI-906
IN V79 CHINESE HAMSTER LUNG CELLS"

RR 745-01330
AUTHOR: ULLOA, H.M. ET AL
DATE: 9-MAY-89
"DERMAL SENSITIZATION STUDY OF CI-906 (QUINAPRIL)
IN GUINEA PIGS (MAXIMIZATION TEST)"

ITEM 12: CASE REPORT FORMS.

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02-JUN-89 CONTENT:	3	LETTER RE: METHOD VALIDATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: REVISED TEST METHODS PER THE TELEPHONE CONVERSATION WITH DONNA CUNNINGHAM. CROSS REFERENCE: DATE - 11-MAY-89
06-JUN-89 CONTENT:		LETTER RE: SAFETY UPDATE LETTER TO: FRIEDMAN, BASIL RE: PROVIDED COPY OF CLINICAL DATA IN SUPPORT OF THE SAFETY UPDATE.
06-JUN-89 CONTENT:		MEMO RE: FDA MEETING MEMO RE: NDA STATUS AS STATED AT 5-JUN-89 FDA MEETING.
08-JUN-89 CONTENT:		FDA CONTACT MEMO MEMO RE: PR. 906-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: CI-906 ADMINISTRATION SCHEDULE FOR PATIENT #2.
08-JUN-89 CONTENT:		LETTER RE: DRUG ADMINISTRATION LETTER TO: FRIEDMAN, BASIL PR. 906-3 RE: PROVIDE CORRECT SCHEDULE.
16-JUN-89 CONTENT:		LETTER FROM FDA RE: MANUFACTURING AND CONTROLS LETTER FROM: LIPICKY, RAYMOND J., M.D. RE: REVIEW HAS BEEN COMPLETED REGARDING THE MANUFACTURING AND CONTROLS PORTION OF THE NDA WITH 12 RECOMMENDATION AND REQUESTS.
22-JUN-89 CONTENT:		FDA CONTACT MEMO MEMO RE: DIASTOLIC BLOOD PRESSURE CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: THE SPECIFIC OF DIASTOLIC BLOOD PRESSURE.

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22-JUN-89
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUINAPRIL, QUINAPRIL/DILTIAZEM AND
PIRMENOL.

CONTACT PERSON: LIPICKY, RAYMOND J.

VERBAL CONVERSATION RE: AFTER 15-JUN-89 MEETING
ON PROCAN SR BID THE FOLLOWING ISSUE WAS
ADDRESSED:

- 1) DEVELOPMENT OF AN ACE INHIBITOR/CALCIUM CHANNEL
- 2) NDAS ON ACE INHIBITORS WOULD NOT BE BROUGHT
BEFORE THE ADVISORY COMMITTEE.

26-JUN-89
CONTENT:

FDA CONTACT MEMO

MEMO RE: EXPORT APPLICATION.

CONTACT PERSON: BECK, ELLIOTT

TELEPHONE CONVERSATION RE: ACUITEL WILL ONLY BE
MARKETED IN BLISTER PACKS IN FRANCE.

28-JUN-89
CONTENT:

LETTER TO: EXPORT APPLICATION

LETTER TO: COOPER, MARY

RE: RESUBMISSION OF EXPORT APPLICATION TO FRANCE.

18-JUL-89
CONTENT:

FDA CONTACT MEMO

MEMO RE: PR. 906-238 AND RR 720-02394

CONTACT PERSON: FRIEDMAN, BASIL

TELEPHONE CONVERSATION RE: SEVERAL QUESTIONS
REGARDING THE STUDY.

18-JUL-89
CONTENT:

LETTER RE: RESPONSE TO VERBAL REQUEST FOR INFORMATION

LETTER TO: FRIEDMAN, BASIL

RE: RESPONSE TO TELEPHONE CONVERSATION REGARDING
A COPY OF VOLUME 106 OF THE NDA TO REPLACE
VOLUME MISSING PAGES.

20-JUL-89
CONTENT:

4

LETTER RE: RESPONSE TO REQUEST FOR INFORMATION

LETTER TO: LIPICKY, RAYMOND J., M.D.

RE: RESPONSE TO DR. BASIL FRIEDMAN REQUEST FOR
INFORMATION. (THREE TELEPHONE REPORTS)

31-JUL-89
CONTENT:

FDA CONTACT MEMO

MEMO RE: EXPORT APPLICATION

CONTACT PERSON: COOPER, MARY F.

TELEPHONE CONVERSATION RE: 28-JUL-89 OF HOW TO
COORDINATE INCLUSION OF ITALY AND UNITED KINGDOM
APPROVALS INTO OUR EXPORT APPLICATION.

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01-AUG-89 CONTENT:	4	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO 16-JUN-89 WRITTEN REQUEST FOR ADDITIONAL INFORMATION REGARDING CHEMISTRY, MANUFACTURING AND CONTROL.
15-AUG-89 CONTENT:		FDA CONTACT MEMO MEMO RE: 9-003-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST EXPLANATION OF APPARENTLY LOW NUMBER OF EVALUABLE PATIENTS.
15-AUG-89 CONTENT:		FDA CONTACT MEMO MEMO RE: 9-003-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL INFORMATION REGARDING THE STUDY.
16-AUG-89 CONTENT:		FDA CONTACT MEMO MEMO RE: 9-003-3 CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL INFORMATION REGARDING EVALUABLE PATIENTS IN STUDY.
24-AUG-89 CONTENT:		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: FRIEDMAN, BASIL PR. 9-003-3 RE: RESPONSE TO 15-AUG-89 AND 16-AUG-89 VERBAL REQUEST FOR ADDITIONAL INFORMATION.
05-SEP-89 CONTENT:		LETTER FROM FDA RE: EXPORT APPROVAL LETTER FROM: MICHELS, DANIEL L. RE: APPROVAL TO EXPORT QUINAPRIL HYDROCHLORIDE (IN BULK FORM: ACUITEL) PACKAGING IS IN BOTTLES OF 5 MG AND 20 MG TABLETS AND UNIT DOSE IN 5 MG AND 20 MG BLISTER PACKAGES TO FRANCE.

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06-SEP-89 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:

LETTER TO: FRIEDMAN, BASIL
PR. 906-12
RE: RESPONSE TO REQUEST FOR ADDITIONAL INFORMATION
REGARDING THE STUDY AS FOLLOWS:
1) HOW ARE PATIENTS WHO RECEIVE BETA BLOCKERS OR
CALCIUM CHANNEL BLOCKERS ASSIGNED TO THE
MONOTHERAPY AND MONOTHERAPY PLUS DIURETIC
CATAGORIES?
2) IDENTIFY INFORMATION IN THE NDA ON PATIENTS
WITH RENAL INSUFFICIENCY.

11-SEP-89 MEMO RE: STATUS OF METHOD VALIDATION
CONTENT:

MEMO TO: DREW, HENRY (FDA, ST LOUIS)
RE: PER TELEPHONE CONVERSATION, THE ANALYSIS
WAS COMPLETED AND THE REPORT WAS FORWARDED
21-AUG-89.

12-SEP-89 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:

LETTER TO: FRIEDMAN, BASIL
PR. 906-12
RE: RESPONSE TO QUESTIONS REGARDING THE OPEN-LABEL
EXTENSION AND THE LOCATION OF INFORMATION ON
PATIENTS WITH RENAL INSUFFICIENCY.

13-SEP-89 5 LETTER RE: AMENDMENT TO NDA
CONTENT:

LETTER TO: LIPICKY, RAYMOND J.
RE: TO PROVIDE ADDITONAL DRUG PRODUCT
MANUFACTURING SITE AND ADDITIONAL PACKAGING
SITE ADDRESSES AND FACILITIES.

15-SEP-89 FDA CONTACT MEMO
CONTENT:

MEMO RE: REVIEW OF THE CLINICAL DATA IN NDA
CONTACT PERSON: FRIEDMAN, BASIL
TELEPHONE CONVERSATION RE: HAVE COMPLETED REVIEW
OF EFFICACY AND SAFETY.

18-SEP-89 FDA CONTACT MEMO
CONTENT:

MEMO RE: PIVOTAL EFFICACY STUDIES
CONTACT PERSON: SEGAL, DORALIE
TELEPHONE CONVERSATION RE: DR. FRIEDMAN'S VERBAL
REQUEST TO HER FOR ADDITIONAL INFORMATION
REGARDING PRS. 906-12, 30 AND 238 AS FOLLOWS:
1) LIST OF INVESTIGATORS.
2) PATIENTS NUMBER UNDER EACH INVESTIGATOR.
3) NUMBER OF PATIENTS COMPLETED UNDER EACH
INVESTIGATOR.

1) NUMBER USED FOR EFFICACY ANALYSIS

- 5) COPY OF THE PROTOCOL.
- 6) BLANK CRF'S.

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18-SEP-89		FDA CONTACT MEMO
CONTENT:		MEMO RE: RANDOMIZATION CODES AND PIVOTAL PROOF OF EFFICACY CONTACT PERSON: FRIEDMAN, BASIL TELEPHONE CONVERSATION RE: REQUEST RULES FOR THE FOLLOWING: 1) BREAKING DOUBLE-BLIND CODES. 2) PROOF OF EFFICACY TO COMPLETE OVERALL SUMMARY.
21-SEP-89		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		LETTER TO: FRIEDMAN, BASIL PRS. 906-82, 238, 9-003-3, 4 AND 9-008-1 RE: RESPONSE TO REQUEST TO DESCRIBE PROCEDURES FOR CODE BREAKING IN THE BLINDED STUDIES.
22-SEP-89		MEMO RE: STATUS OF METHOD VALIDATION
CONTENT:		MEMO TO: SCHNEIDER, FELIX (FDA, DETROIT) RE: THE ANALYSIS WAS COMPLETED AND THE REPORT WILL BE SENT 25-SEP-89.
03-OCT-89		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		LETTER TO: SEGAL, DORALIE PRS. 906-12, 30 AND 238 RE: RESPONSE TO 18-SEP-89 REQUEST FOR INFORMATION REGARDING THE FOLLOWING: 1) LIST OF PRINCIPLE INVESTIGATORS. 2) PATIENT INFORMATION. 3) COPY OF PROTOCOL. 4) BLANK CASE REPORT FORMS.
03-OCT-89	6	LETTER RE: VERBAL REQUEST FOR INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. PRS. 906-12, 30 AND 238 RE: 18-SEP-89 TELEPHONE CONVERSATION WITH DORALIE SEGAL REQUESTING THE FOLLOWING ON PIVOTAL STUDIES: 1) LIST OF PRINCIPAL INVESTIGATORS. 2) PATIENT INFORMATION. 3) COPY OF PROTOCOLS. 4) BLANK CASE REPORT FORMS.

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13-OCT-89
CONTENT:

MEMO RE: FDA STUDY SITES AUDITS

MEMO RE: TELEPHONE CONVERSATION WITH MS. SEGAL
REGARDING THE VERIFICATION OF RECEIPT OF
INVESTIGATOR AND PATIENT INFORMATION
SENT 5-OCT-89 FOR FDA AUDIT.

19-OCT-89
CONTENT:

2 EXPORT APPLICATION

END-0058
ITALY
GREAT BRITAIN

15-NOV-89
CONTENT:

LETTER FROM FDA RE: EXPORT APPROVAL

LETTER FROM: MICHELS, DANIEL
RE: APPROVAL TO EXPORT QUINAPRIL TO ITALY AND
THE UNITED KINGDOM.

06-DEC-89
CONTENT:

3 EXPORT APPLICATION

END-0058
ITALY
UNITED KINGDOM

21-DEC-89
CONTENT:

LETTER FROM FDA RE: EXPORT APPROVAL

LETTER FROM: MICHELS, DANIEL L.
RE: APPROVED THE EXPORTATION OF QUINAPRIL
HYDROCHLORIDE BULK FORM TO ITALY AND
THE UNITED KINGDOM.

02-JAN-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: SAFETY REPORT
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: CONFIRMING THE RECEIPT
OF THE 10-DAY SAFETY REPORT.

02-JAN-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: GENERAL INFORMATION
CONTACT PERSON: FRIEDMAN, BASIL
TELEPHONE CONVERSATION RE: INFORMED HIM THAT
DR. VILLAUME HAS LEFT THE COMPANY AND INQUIRED
HOW DR. LIPICKY'S REVIEW WAS GOING.

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03-JAN-90 LETTER RE: INTERNATIONAL DRUG OBJECTION
CONTENT:

LETTER TO: AHLGREN, KARIN
RE: SWEDEN HAS OBJECTED TO QUINAPRIL IN THE
COUNTRY. RESEARCH REPORTS WERE PROVIDED FOR
THE RESPONSES OF THE OVERALL ASSESSMENT FROM
THE SWEDISH REGULATORY AUTHORITY.

05-JAN-90 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:

LETTER TO: AHLGREN, KARIN
RE: PROVIDED RESEARCH REPORTS THAT WERE MISSING
FROM OTHER INFORMATION SECTION IN THE MAA.

10-JAN-90 LETTER RE: GENERAL INFORMATION
CONTENT:

LETTER TO: AHLGREN, KARIN
RE: DRAFT COPY ON THE EUROPEAN SYMPOSIUM ON
BIOAVAILABILITY ALONG WITH RR X-745-01381.

12-JAN-90 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:

LETTER TO: AHLGREN, KARIN
RE: RESPONSE TO CONCERNS REGARDING SWEDISH DRA
QUESTIONS.

19-JAN-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: NDA STATUS
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE:
1) DR. TRAN IS THE BIOPHARMACEUTIC REVIEWER.
2) THE CLINICAL DATA HAS NOT BEEN REVIEWED YET.
3) THE PRECLINICAL REVIEW IS UNDERWAY.

09-FEB-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: TROUGH BLOOD PRESSURE MEASUREMENT
CONTACT PERSON: FRIEDMAN, BASIL
TELEPHONE CONVERSATION RE: CONCERNS ABOUT THE
TROUGH BLOOD PRESSURE MEASUREMENT IN BID
STUDY 9-003-3.

13-FEB-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: DR. FRIEDMAN'S REQUEST INFORMATION
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL
INFORMATION REGARDING THE RECENT CLINICAL STUDY
REPORTS SUBMITTED TO THE QUINAPRIL IND.

CONFERENCE CALL RE: UPDATING OUR EFFICACY DATA

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21-FEB-90		LETTER RE: GENERAL INFORMATION
CONTENT:		LETTER TO: TSUI, D. RE: PROVIDED PROTOCOL REGARDING THE BIOAVAILABILITY OF QUINAPRILAT FOLLOWING ORAL ADMINISTRATION OF QUINAPRIL.
14-MAR-90		LETTER RE: VERBAL REQUEST FOR MEETING
CONTENT:		LETTER TO: FRIEDMAN, BASIL RE: TELEPHONE CONVERSATION ON 12-MAR-90 REQUESTING MEETING TO REVIEW TIME WINDOW FOR TROUGH BLOOD PRESSURE MEASUREMENTS. MEETING SCHEDULED 20-MAR-90.
26-MAR-90		LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:		LETTER TO: TSUI, D. RE: RESPONSE TO ISSUES RAISED BY AUSTRALIAN DRA ON QUINAPRIL APPLICATION.
29-MAR-90	7	MINUTES OF FDA MEETING
CONTENT:		DATE: 20-MAR-90 MEETING WITH DR. FRIEDMAN RE: TO REVIEW THE TIME WINDOW FOR TROUGH BLOOD PRESSURE MEASUREMENTS.
29-MAR-90	8	LETTER RE: RESPONSE TO VERBAL REQUEST FOR INFORMATION
CONTENT:		LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO 19-JAN-90 AND 14-MAR-90 TELEPHONE CONVERSATION REGARDING MOUSE AND RAT CARCINOGENICITY BIOASSAYS FOR USE BY DR. VANARSDEL.
04-APR-90		MEMO RE: TRIP REPORT
CONTENT:		MEMO RE: TRIP REPORT REGARDING 3-MAR-90 MEETING WITH FDA.
06-APR-90		MEMO RE: NDA REVIEW
CONTENT:		MEMO RE: NDA BIOPHARMACEUTICS REVIEW OF THE NDA.

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06-APR-90 CONTENT:	10	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO SEVERAL REQUESTS FOR INFORMATION.
17-APR-90 CONTENT:	9	LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS LETTER TO: LIPICKY, RAYMOND J., M.D. RE: UPDATED CHEMISTRY; MANUFACTURING AND CONTROLS DATA.
20-APR-90 CONTENT:		LETTER RE: MEETING CONFIRMATION LETTER TO: WOLTER, ROBERT RE: CONFIRMATION OF MEETING TO BE HELD 7-MAY-90 TO DISCUSS DESIGNATION OF STARTING MATERIAL IN THE SYNTHESIS OF QUINAPRIL HYDROCHLORIDE.
26-APR-90 CONTENT:		MEMO RE: FDA VISIT MEMO RE: VISIT WITH BONGIOVANNI, KATHLEEN REGARDING THE FOLLOWING: 1) CONFIRMATION OF 7-MAY-90 MEETING. 2) FINAL SAFETY UPDATE IS PLANNED FOR COMPLETION IN JUNE WITH SUBMISSION IN JULY.
10-MAY-90 CONTENT:		LETTER FROM FDA RE: MINUTES OF FDA MEETING LETTER FROM: MORGENSTERN, NATALIA A. DATE: 28-NOV-89 FDA MEETING RE: PRE-NDA MEETING FOR QUINAPRIL/HCTZ COMBINATION PRODUCT.
15-MAY-90 CONTENT:		FDA CONTACT MEMO MEMO RE: CHEMISTRY CONTACT PERSON: WOLTERS, ROBERT FDA MEETING RE: DISCUSSION WITH CHEMISTRY REVIEWER CONCERNING QUINAPRIL.
18-MAY-90 CONTENT:		FDA CONTACT MEMO MEMO RE: NDA AND SBA CONTACT PERSON: RESNICK, CHARLES TELEPHONE CONVERSATION RE: FOLLOW-UP TO MEETING REQUEST ON 7-MAY-90 REGARDING CONFLICTING REPORTS FROM THE AGENCY CONCERNING SCALE-UP LOT REQUIREMENTS FOR NCE NDAS.

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18-MAY-90 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP ON MEETING CONTACT PERSON: WOLTERS, R. TELEPHONE CONVERSATION RE: FOLLOW-UP TO 7-MAY-90 MEETING.
21-MAY-90 CONTENT:		FDA CONTACT MEMO MEMO RE: NDA REVIEW CONTACT PERSON: HUANG, MEI-YING NG, TIE-HUA CHEN, SHAW FDA MEETING RE: STATUS OF PENDING NDA REVIEWS.
01-JUN-90 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP ON SUBMISSION CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: FOLLOW-UP ON REQUEST FOR INFORMATION REGARDING 18-MAY-90 SUBMISSION.
04-JUN-90 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO CONVERSATION CONTACT PERSON: GRAHAM, CHERYL FDA MEETING RE: FOLLOW-UP TO 1-JUN-90 CONVERSATION WITH KATHLEEN BONGIOVANNI.
11-JUN-90 CONTENT:		FDA CONTACT MEMO MEMO RE: HOLD ON MEETING CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: HER MEETING WITH DRS. CHEN, GRAHAM AND CHEN WILL WAIT TILL THE COMPLETION OF ALL REVIEWS.
13-JUN-90 CONTENT:		MEMO RE: SUMMARY OF NDA AND MAA MEMO RE: CLINICAL SUMMARIES FOR QUINAPRIL NDA AND TACRINE MAA.
18-JUN-90 CONTENT:		FDA CONTACT MEMO MEMO RE: FDA FIELD INSPECTION OF PIVOTAL STUDY SITES. CONTACT PERSON: DR. ELHAGE TELEPHONE CONVERSATION RE: MS. DORALIE SEGAL HAS LEFT THE AGENCY AND THE FDA INSPECTION FOR SITES 906-12 AND 30 HAS BEEN DELAYED.

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25-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: REQUEST FDA MEETING CONTACT PERSON: VANARSDALE, W TELEPHONE CONVERSATION RE: REQUEST FDA MEETING ON 27-JUN-90.
28-JUN-90		MEMO RE: CSA
CONTENT:		MEMO RE: CSA FOR PR. 906-345. PROVIDED ADDITIONAL INFORMATION IN SUPPORT OF CSA FOR QUINAPRIL/DILITAZE.
29-JUN-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO VERBAL REQUEST CONTACT PERSON: RESNICK, CHARLES TELEPHONE CONVERSATION RE: REQUEST ADDITIONAL PHARMACOLOGY REPORTS AND DRAFT SBA.
06-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA REVIEWS CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: REQUEST STATUS OF NDA REVIEW. SHE REQUESTED A DESK COPY OF THE REVISED LABELING.
06-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF REVIEW CONTACT PERSON: LIPICKY, RAYMOND J. TELEPHONE CONVERSATION RE: QUESTIONS REGARDING QUINAPRIL REVIEW STATUS. SBA FORMAT MEETING SCHEDULED FOR 10-JUL-90.
10-JUL-90		LETTER FROM FDA RE: REQUEST INFORMATION
CONTENT:		LETTER FROM: MORGENSTERN, NATALIA A. RE: QUESTIONS RAISED FROM REVIEWING SUBMISSION OF 26-JAN-89.
13-JUL-90		FDA CONTACT MEMO
CONTENT:		MEMO RE: CLINICAL INSPECTION AND SBA CONTACT PERSON: BONGIOVANNI, KATHLEEN FDA MEETING TO FOLLOW-UP THE 10-JUL-90 DISCUSSION REGARDING CLINICAL INSPECTION AND SBA.

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13-JUL-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: NDAS
CONTACT PERSON: WOLTERS, ROBERT
FDA MEETING TO DISCUSS QUESTIONS ON PENDING
QUINAPRIL NDA AND FUTURE Q/HCTZ NDA EA.

13-JUL-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: SBA
CONTACT PERSON: RESNICK, CHARLES
FDA MEETING TO DISCUSS THE FORMAT OF SBA FOR
PRECLINICAL SECTION.

18-JUL-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: REQUEST INFORMATION
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: REQUEST PROTOCOL
NUMBERS FOR INVESTIGATORS TO BE AUDITED.

20-JUL-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: DRAFT SBA
CONTACT PERSON: RESNICK,
TELEPHONE CONVERSATION RE: REQUEST HIS OPINION
ON THE DRAFT SBA FORMAT AND HIS LISTED SPECIFIC
COMMENTS.

24-JUL-90
CONTENT:

MINUTES OF FDA MEETING

DATE: 10-JUL-90
FDA MEETING RE: TO DISCUSS THE SBA.

25-JUL-90
CONTENT:

11 SAFETY UPDATE
VOLUMES=34

25-JUL-90
CONTENT:

12 LETTER RE: PACKAGE INSERT
LETTER TO: LIPICKY, RAYMOND J.
VOLUMES=7
RE: PACKAGE INSERT.

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31-JUL-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRMATION OF SAFETY UPDATE
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: CONFIRMATION OF RECEIPT
OF SAFETY UPDATE AND REVISED PACKAGE INSERT.

06-AUG-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: REQUEST FOR INFORMATION
CONTACT PERSON: SAMARA, DR.
TELEPHONE CONVERSATION RE: QUESTIONS DURING
NDA REVIEW.

07-AUG-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP
CONTACT PERSON: SAMARA, DR.
TELEPHONE CONVERSATION RE: FOLLOW-UP TO 6-AUG-90
REQUEST FOR ADDITIONAL INFORMATION.

08-AUG-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: SAFETY UPDATE
CONTACT PERSON: FREIDMAN, BASIL
TELEPHONE CONVERSATION RE: SECOND SAFETY UPDATE.

09-AUG-90

13-AUG-90 ANNUAL REPORT
CONTENT:

END-0058
END-0058A01
END-0058A02

14-AUG-90 14 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:
LETTER TO: LIPICKY, RAYMOND J.
RE: RESPONSE TO BIOPHARMACEUTICS QUESTIONS ON
QUINAPRIL NDA.

17-AUG-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO SBA
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: FOLLOW-UP TO
SENDING OF DRAFT FIGURES FOR SBA.

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21-AUG-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS
CONTACT PERSON: BONGIOVANNI, KATHLEEN
MEETING WITH FDA RE: PENDING NDA. THE FOLLOWING
WAS DISCUSSED:

- 1) THE BIOPHARM. IS ACTIVELY BEING REVIEWED.
- 2) THE BIOSTAT. HAS BEGUN HIS REVIEW.
- 3) DR. FRIEDMAN HAS COMPLETED HIS REVIEW OF THE
SAFETY UPDATE AND THE SECONDARY REVIEW SHALL
BEGIN.
- 4) WE ARE WORKING ON BOTH THE PRECLINICAL AND
CLINICAL SBAS.

21-AUG-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP ON REQUEST
CONTACT PERSON: SAMARA, DR.
MEETING WITH FDA RE: HIS REVIEW OF THE QUINAPRIL
NDA BIOPHARM. SECTION.

22-AUG-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: SBA
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: REVIEW OF DRAFT
FIGURES FOR QUINAPRIL SBA.

31-AUG-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS REPORT
CONTACT PERSON: CUNNINGHAM, DANUTE
TELEPHONE CONVERSATION RE: STATUS OF REQUEST
FOR INSPECTION OF MANUFACTURING SITES.

31-AUG-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: MANUFACTURING STATUS
CONTACT PERSON: CUNNINGHAM, DANUTE
TELEPHONE CONVERSATION RE: STATUS OF REQUEST FOR
INSPECTION OF MANUFACTURING SITES.

21-SEP-90
CONTENT:

15 LETTER RE: SUMMAY BASIS OF APPROVAL

LETTER TO: LIPICKY, RAYMOND J.
RE: PROVIDED A DRAFT SUMMARY BASIS OF APPROVAL FOR
FDA'S REVIEW AND COMMENTS

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27-SEP-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: SBA RECEIPT CONFIRMATION
CONTACT PERSON: RESNICK, CHARLES
TELEPHONE CONVERSATION RE: REQUEST CONFIRMATION
OF RECEIPT OF SBA AND CHECK STATUS OF NDA REVIEW.
SBA WAS NOT RECEIVED, ANOTHER COPY OF THE SBA
WAS SENT.

27-SEP-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: MEETING REQUEST
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: REQUEST MEETING TO
ASSESS THE REALISTIC PROBABILITY FOR A 1990
APPROVAL FOR QUINAPRIL.

28-SEP-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO MEETING REQUEST
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CALL RE: OFFERED 12-OCT-90, 3 PM FOR
MEETING TO ASSESS THE REALISTIC PROBABILITY FOR
A 1990 APPROVAL FOR QUINAPRIL. DATE WAS
ACCEPTED.

01-OCT-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRMATION OF RECEIPT
CONTACT PERSON: SECRETARY TO RESNICK, C.
TELEPHONE CONVERSATION RE: TO CONFIRM RECEIPT OF
DRAFT SBA PLUS COMPUTER DISKETTE.

09-OCT-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS OF PHARMACOLOGY REVIEW
CONTACT PERSON: RESNICK, CHARLES
VISITED FDA RE: THE RECENTLY SUBMITTED SBA AND
THE STATUS OF DR. VANARSDALE'S REVIEW OF THE
QUINAPRIL NDA.

09-OCT-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRM MEETING/STATUS CHECK
CONTACT PERSON: BONGIOVANNI, KATHLEEN
VISITED FDA RE: CONFIRMATION OF 12-OCT-90 FDA
MEETING WITH DR. LIPICKY AND THE STATUS OF THE
REVIEWS.

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17-OCT-90 CONTENT:		FDA CONTACT MEMO MEMO RE: REVIEW OF DRAFT SBA CONTACT PERSON: CHEN, SHAW, DR. VISITED FDA RE: REQUEST MINOR RE-WORDINGS OR ADDITIONAL DETAILS OR EXPLANATIONS AS FOLLOWS: 1) A MORE DETAILED JUSTIFICATION FOR THE ONCE DAILY SLOW TITRATION STATEMENT. 2) A LISTING OF DEATHS/WITHDRAWALS DURING THE CONTROLLED STUDY PERIODS VS. CONTROLS BROKEN OUT FOR HYPERTENSION AND CHF SEPARATELY. 3) A LISTING OF SERIOUS AES DURING CONTROLLED PERIODS VS. PLACEBO AND ACTIVE CONTROLS. 4) PROPOSED LABELING ACCOMPANY THE SBA.
24-OCT-90 CONTENT:		FDA CONTACT MEMO MEMO RE: QUESTIONS ON SBA CONTACT PERSON: FREEDMAN, BASIL, DR. TELEPHONE CONVERSATION RE: REQUEST STATUS OF REVIEW OF THE SBA. HE HAS FINISHED HIS REVIEW AND WAS WRITING HIS COMMENTS.
25-OCT-90 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO 24/OCT/90 FDA CONTACT MEMO CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: INFORMED HER OF CONVERSATION WITH DR. FREEDMAN REGARDING THE SBA.
25-OCT-90 CONTENT:	16	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO MS. KATHLEEN BONGIOVANNI SURVEY FORM REGARDING STUDIES IN PEDIATRIC PATIENTS.
30-OCT-90 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO TELEPHONE CALL CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO TELEPHONE CONVERSATION RE: FOLLOW-UP TO 25-OCT-90 TELEPHONE CALL.
31-OCT-90 CONTENT:	17	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION LETTER TO: LIPICKY, RAYMOND J., M.D. VOLUME=10 RE: RESPONSE TO 10-JUL-90 MEETING REQUEST REGARDING THE SUMAMRY BASIS OF APPROVAL (SBA) SECTIONS 2, 3, 5, 6 AND 8 ARE AMENDED. ITEM 1: AMENDMENT TO SECTION 2, COMPREHENSIVE SUMMARY

ITEM 2: AMENDMENT TO SECTION 3, CHEMISTRY,
MANUFACTURING AND CONTROLS.
ITEM 3: AMENDMENT TO SECTION 5, NONCLINICAL
PHARMACOLOGY AND TOXICOLOGY.

RR 740-02536
AUTHOR: RAPUNDALO, S. ET AL
DATE: 31-AUG-89
"COMPARATIVE EFFECTS OF QUINAPRIL AND QUINAPRILAT
ON VARIOUS PROTEINASES"

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31-OCT-90	17	LETTER - CONTINUED
CONTENT:		<p>RR 740-02796 AUTHORS: RYAN, M.J. OLSZEWSKI, B.J. DATE: 26-FEB-90 "ANTIHYPERTENSIVE ACTIVITY OF QUINAPRIL GIVEN FOR 14 DAYS TO CONSCIOUS SPONTANEOUSLY HYPERTENSIVE RATS"</p> <p>RR 740-02694 AUTHOR: CASAD, B. ET AL DATE: 1-SEP-89 "A MULTIPLE-DOSE STUDY TO ASSESS THE FUNCTIONAL INTERACTION OF QUINAPRIL (CI-906) AND HYDROCHLOROTHIAZIDE (CI-570) IN SALINE-LOADED SPONTANEOUSLY HYPERTENSIVE RATS"</p>
31-OCT-90	17	LETTER - CONTINUED
CONTENT:		<p>RR 4192-00422 AUTHOR: NEUB, M. ET AL DATE: 23-APR-90 "DOSE-PROPORTIONALITY AND SYSTEMIC EXPOSURE OF QUINAPRILAT IN MICE AND RATS FOLLOWING MULTIPLE ORAL DOSES OF QUINAPRIL (PRECLINICAL PROTOCOLS 90-001 AND 90-002)"</p> <p>ITEM 4: AMENDMENT TO SECTION 6, HUMAN PHARMACOKINETIC AND BIOAVAILABILITY.</p> <p>RR 764-00523 AUTHOR: FERRY, J. ET AL DATE: 16-MAY-86 "CLINICAL BIOPHARMACEUTICAL STUDY OF TWO NEW PROTOTYPE FORMULATION CAPSULES OF QUINAPRIL (CI-906) AND AN IMMEDIATE-RELEASE CAPSULE PROTOCOL 906-81"</p>
31-OCT-90	17	LETTER - CONTINUED
CONTENT:		<p>ITEM 5: AMENDMENT TO SECTION 8, CLINICAL DATA.</p> <p>RR 720-02593 AUTHOR: CANTER, D. ET AL DATE: 25-APR-90 "AN EIGHT-WEEK, PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTICENTER STUDY TO EVALUATE THE DOSE RESPONSE RELATIONSHIP OF QUINAPRIL (CI-906) WITH CONCOMITANT HYDROCHLOROTHIAZIDE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION. (PROTOCOL 906-241 THROUGH -19, -22 THROUGH -25, AND -27 THROUGH -35)"</p> <p>RR MEMO-420-00165 AUTHOR: RAULE, G. DATE: 12-MAR-90</p>

"QUINAPRIL IN HYPERTENSIVE PATIENTS WITH BRONCHIAL
ASTHMA, DOUBLE-BLIND, ACUTE TEST VERSUS ENALAPRIL
AND 12-WEEK FOLLOW-UP. (PROTOCOL 906-307,
INTERIM REPORT)"

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31-OCT-90	18	LETTER RE: SECOND DRAFT SUMMARY BASIS OF APPROVAL
CONTENT: LETTER TO: LIPICKY, RICHARD J., M.D. RE: SECOND DRAFT OF THE SUMMARY BASIS OF APPROVAL PER 10-JUL-90 MEETING REQUEST.		
01-NOV-90		FDA CONTACT MEMO
CONTENT: MEMO RE: DESK COPY OF DRAFT SBA CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO VISITED FDA RE: 1) SBA. 2) NDA AMENDMENT - PRECLINICAL AND CLINICAL REPORTS THAT ARE OUTSTANDING. 3) LABELING. 4) MEDICAL REVIEWER'S COMMENTS. 5) BIOMETRICS.		
02-NOV-90		LETTER RE: SBA
CONTENT: LETTER TO: FRIEDMAN, BASIL, M.D. RE: SECOND DRAFT SUMMARY BASIS OF APPROVAL.		
02-NOV-90	19	LETTER RE: DRAFT LABELING
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. RE: A RUNNING TEXT OF THE DRAFT PACKAGE INSERT.		
06-NOV-90		FDA CONTACT MEMO
CONTENT: MEMO RE: FOLLOW-UP TO 1/NOV/90 VISIT CONTACT PERSON: BONGIOVANNI, KATHLEEN TELEPHONE CONVERSATION RE: FOLLOW-TO TO VISIT REGARDING THE FOLLOWING: 1) SBA - DR. FRIEDMAN HAS RECEIVED HIS COPY. 2) NDA AMENDMENT - BIOPHARMACEUTICAL SECTION AND LABELING. 3) LABELING - COULD SUBMIT F.P.L. IF WE WISHED. 4) MEDICAL REVIEWER'S COMMENTS - SUGGESTED WE MAKE A REQUEST FOR INFORMATION IMMEDIATELY. 5) BIOMETRICS - SHE PROMISED TO FOLLOW-UP ON THE STATUS OF THE REVIEW.		
07-NOV-90	20	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D. RE: RESPONSE TO DR. BASIL FRIEDMAN'S COMMENTS REGARDING THE FOLLOWING: 1) QUINAPRIL IN PATIENTS WITH RENAL DYSFUNCTION. 2) ANALYSIS OF EFFICACY DATA WITH DBP > 95 VS. > 100 MM HG. 3) PROCEDURE FOR DOUBLE-BLIND CODE BREAKING. 4) QUINAPRIL DOSE RESPONSE. 5) QUALITY OF STUDY CONDUCT		

- 6) EFFICACY - QUINAPRIL QD VS BID REGIMEN.
- 7) ADVERSE EVENTS - QUINAPRIL QD VS BID REGIMENS.
- 8) TIME-WINDOW FOR BID DOSING EVALUATION.
- 9) ADDITIONAL EFFICACY WITH DIURETIC THERAPY.
- 10) NONDIURETIC ANTIHYPERTENSIVE THERAPY IN
LONG-TERM STUDIES.

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09-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: UPDATE ON STATUS OF RESEARCH REPORTS
SENT TO FDA
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: TO INFORM HER THAT THE
FINAL TWO RESEARCH REPORTS WERE SHIPPED 12/NOV/90
AND ASKED IF WE COULD SEND A COPY DIRECTLY TO
DR. FRIEDMAN. SHE STATED "NO" AND SUGGESTED WE
SEND A EXTRA COPY TO FDA, MARKED FOR DR. FIREDMAN
REVIEW.

09-NOV-90 21 INFORMATION AMENDMENT
CONTENT:
REVISED PAGES DRAFT SUMMARY BASIS OF APPROVAL
PGS. 235 AND 238
CROSS REFERENCE: REFERENCE #18

09-NOV-90 22 INFORMATION AMENDMENT
CONTENT:
RR MEMO-710-02839
AUTHOR: CANTER, D.A. ET AL
DATE: 9-NOV-90
"INITIAL SUMMARY OF RESULTS ON THE DOSE
RESPONSE RELATIONSHIP, HUMORAL EFFECTS AND
PHARMACOKIENTICS OF QUINAPRIL IN SALT-REplete
NORMOTENSIVE SUBJECTS (PROTOCOL 906-296)"

RR 720-02788
AUTHOR: BEAMAN, B.A. ET AL
DATE: 9-NOV-90
"A 12-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED,
PARALLEL-GROUP, RANDOMIZED STUDY COMPARING
THE ANTIHYPERTENSIVE EFFECTS OF ONCE DAYLY
DOSES OF QUINAPRIL HYDROCHLORIDE (CI-906) WITH
PLACEBO ON 24-HOUR BLOOD PRESSURE IN PATIENTS
WITH MILD TO MODERATE HYPERTENSIVE (PROTOCOL
906-327)"

11-NOV-90 FDA CONTACT MEMO
CONTENT:
MEMO RE: STATUS OF REVIEW OF SBA
CONTACT PERSON: CHEN, SHAW, DR.
VISITED FDA RE: STILL REVIEWING THE FIRST VERSION
OF THE SBA. HIS OVERALL IMPRESSION OF THE NDA
IS THAT IT IS CLEARLY APPROVABLE FOR BID DOSING,
BUT HAD NOT MADE HIS DECISION REGARDING ONCE-A-
DAY YET.

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12-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTION ON 906-327 CLINICAL REPORT.
CONTACT PERSON: FRIEDMAN, BASIL, DR.
TELEPHONE CONVERSATION RE: QUESTION ON THE FINAL
REPORT OF -327; TROUBLE FINDING SUPPORTIVE
DOCUMENTATION IN THE APPENDICES FOR A FEW
SUMMARY TABLES.

13-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTION ON RESEARCH REPORT FOR STUDY
906-114
CONTACT PERSON: CHEN, SHAW, DR.
TELEPHONE CALL FROM FDA RE: REQUESTED
CLARIFICATION ON THE FOLLOWING:
1) THE NUMBER OF PATIENTS INCLUDED IN THE
DIFFERENT ANALYSES SUMMARIZED ON TABLE 14.
2) DIFFERENCE BETWEEN THE INTENT-TO-TREAT AND
THE WEEKS 1 - 8 SAMPLES.
3) COMMENT: HE HAD NOT YET REVIEWED THE
REVISED DRAFT OF THE SBA.

15-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: REQUEST MEETING, REQUEST INFORMATION
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: REQUEST THE
FOLLOWING:
1) MEETING TO DISCUSS THE STATUS OF THE NDA.
MEETING WAS GRANTED FOR 16-NOV-90 AT 1 PM.
2) MS BONGIOVANNI CALLED BACK WITH A QUESTION
FROM DR. FRIEDMAN. HE REQUESTED THE
SUBMISSION WHICH CONTAINED CLINICAL REPORTS
OF -296 AND -327.
SUBMISSION WAS SENT 9-NOV-90. SHE SHALL
CHECK WITH THE DOCUMENT ROOM AND DR. FRIEDMAN.

15-NOV-90 LETTER FROM FDA RE: REQUEST INFORMATION
CONTENT:

LETTER FROM: HUNG, H.M. JAMES, PH.D.
PR. 906-12
RE: REQUEST BLOOD PRESSURE DATA FOR THE FOLLOWING
ANALYSES:
1) INTENT-TO-TREAT
2) INTENT-TO-TREAT, TIME WINDOW
3) EVALUABLE PATIENTS, BASELINE TO LAST VISIT
4) EVALUABLE PATIENTS, BASELINE TO LAST VISIT >=
WEEK 4

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CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA
CONTACT PERSON: BONGIOVANNI, KATHLEEN
VISITED FDA RE: OFFERED A COPY OF THE LETTER FROM
THE REVIEWING STATISTICIAN. DR. HUNG REQUESTED
DATA FROM 906-12 ON IBM DISKS.

19-NOV-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: FURTHER COMMENTS ON DR. FRIEDMAN'S REVIEW
OF QUINAPRIL SBA
CONTACT PERSON: CHEN, SHAW
TELEPHONE CONVERSATION RE: FURTHER REVIEW OF FDA'S
COMMENTS ON THE SBA AS FOLLOWS:
1) CHANGES COULD BE MADE AFTER APPROVAL.
2) Q.D. IS BETTER THAN PLACEBO. IS IT UNIFORM
ENOUGH?

20-NOV-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: TO PURSUE INSPECTION OF MOPS.
CONTACT PERSON: KUMKUMIAN, CHARLES, DR.
FDA MEETING RE: PER COMMISSIONER'S OFFICE, THE
COMPLIANCE OFFICE HAS NOT RECIEVED THE REQUEST
FOR INSPECTION FROM THE OFFICE OF DRUGS.
DR. KUMKUMIAN PROMISED TO LOOK INTO THIS MATTER.

20-NOV-90
CONTENT:

23 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
LETTER TO: HUNG, H.M. JAMES, PH.D.
RE: RESPONSE TO 15-NOV-90 WRITTEN REQUEST FOR
AN IBM READABLE DATA DISKETTE FOR STUDY
906-12.

21-NOV-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO 20/NOV/90 VISIT
CONTACT PERSON: KUMKUMIAN, CHARLES, DR.
VISITED FDA RE: TO INQUIRE ABOUT THE REQUEST
FOR INSPECTION IN OCTOBER AND THAT QUINAPRIL
WAS NOW ON A PRIORITY LIST OF NEW DRUG DIVISIONS.
FDA REQUEST CALL AFTER THE HOLIDAY TO CHECK
ON THE REPORT FROM COMPLIANCE.

26-NOV-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM RECEIPT OF COMPUTER DISKETTES
CONTACT PERSON: HUNG, JAMES, PHD
TELEPHONE CONVERSATION RE: CONFIRM RECEIPT
OF REQUESTED DATA ON STUDY 906-12.

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26-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO 20/NOV/90 VISIT
CONTACT PERSON: KUMKUMIAN, CHARLES, DR.
TELEPHONE CONVERSATION RE: THE OFFICE OF
COMPLIANCE HAS ASSURED HIM THAT QUINAPRIL
WAS ON A SPECIAL PRIORITY INSPECTION LIST.

26-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: COMMENTS ON SECOND DRAFT OF SBA
CONTACT PERSON: CHEN, SHAW, DR.
TELEPHONE CALL FROM FDA RE: REQUEST CHANGES ON
THE SECOND DRAFT OF THE SBA. ALSO REQUESTED
THE FOLLOWING:
1) ADVERSE EVENTS BROKEN DOWN BY DOSE.
2) SBA REPLACEMENT PAGES ARE ACCEPTABLE.

27-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: UPDATE ON NDA ACTIVITIES
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO
TELEPHONE CONVERSATION RE: INFORMED FDA THAT
ALL REQUESTED CHANGES TO THE SBA WOULD ARRIVE
THE NEXT DAY. ADVISED THAT THE 13-DEC-90
ADVISORY COMMITTEE MEETING WOULD BE OF GREAT
INTEREST TO US AND SUGGESTED OUR ATTENDANCE.

27-NOV-90 24 LETTER RE: REVISIONS TO SUMMARY BASIS OF APPROVAL
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.
RE: RESPONSE TO 24-OCT-90 TELEPHONE CONVERSATION
WITH DR. BASIL FREEDMAN REQUESTING REVISIONS
TO THE SUMMARY BASIS OF APPROVAL. ADDITIONAL
RESPONSE TO 26-NOV-90 QUESTIONS FROM DR. CHEN.

29-NOV-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: FINAL COMMENTS ON SBA
CONTACT PERSON: CHEN, SHAW, DR.
TELEPHONE CALL FROM FDA RE: HAD RECEIVED AND
REVIEWED 27-NOV-90 SUBMISSION OF REPLACEMENT
PAGES FOR THE SBA. ONE QUESTION ON THE
REPLACEMENT PAGES AND FOUR ADDITIONAL COMMENTS
ON THE SECOND DRAFT OF THE SBA.

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29-NOV-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUESTION CONCERNING CARCINOGENICITY DATA
CONTACT PERSON: ALI, MIRZA, DR.
TELEPHONE CALL FROM FDA RE: INQUIRED THE
FOLLOWING:
FDA: WHAT THE CAUSE OF DEATH CODE #4 "ANIMAL WAS
SACRIFICED" MEANT?
PARKE-DAVIS: CONFERRED WITH TOXICOLOGY, AND
RETURNED CALL STATING CODE IN QUESTION MEANT
THAT THE ANIMAL WAS SACRIFICED AT A
SCHEDULED SACRIFICE.

03-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF CHEN/LIPICKY REVIEW
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: REVIEWED THE FOLLOWING:
1) ALL OF DR. CHEN'S COMMENTS HAD BEEN ADDRESSED.
2) FDA INQUIRED WHEN OUR LAST SAFETY UPDATED WAS
SUBMITTED. (SUBMITTED 25-JUL-90)
3) FDA CALLED BACK TO CONFIRM SUBMISSION OF THE
SAFETY UPDATE.
4) FDA CALLED TO STATE THAT DR. CHEN WAS NOW
REVIEWING OUR PACKAGE INSERT.

03-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUESTION ON REVIEW
CONTACT PERSON: CHEN, SHAW, DR.
TELEPHONE CALL FROM FDA RE: REQUESTED SPECIFIC
LOCATIONS FOR PEAK B.P. MEASUREMENTS IN THE
FOLLOWING PROTOCOLS:
1) 906-11
2) 906-30
3) 906-114

04-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: NDA STATUS
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: UNABLE TO FLY TO
WASHINGTON LAST NIGHT, SENT OVERNIGHT TO DR. CHEN
SUMMARY TABLES SELECTED FROM PREVIOUSLY SUBMITTED
CLINICAL REPORTS.

05-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: REVIEW OF ACCUPRIL PATIENT INFORMATION
BOOKLET
CONTACT PERSON: FEATHER, KEN
TELEPHONE CONVERSATION RE: REQUEST FEEDBACK ON A
PATIENT INFORMATION BOOKLET WHICH CONTAINS NO
LABELING AND LITTLE MENTION OF QUINAPRIL. SHALL
DROP THE PIECE OFF AT HIS OFFICE ON FRIDAY

7-DEC-90.

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06-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONVEY DR. LIPICKY'S REQUEST FOR
SAFETY UPDATE
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO
TELEPHONE CALL RE: DR. KIPICKY DOES WANT A SAFETY
UPDATE PRIOR TO APPROVAL. THE UPDATE IS NEEDED
POST-APPROVALBE, BUT WOULD BE REQUIRED PRIOR TO
FINAL APPROVAL.

06-DEC-90 25 LETTER RE: PROPOSED PACKAGE INSERT
CONTENT:

LETTER TO: LIPICKY, RAYMOND J., M.D.
CI-906
RE: RESPONSE TO FDA REQUEST FOR INFORMATION
REGARDING MORE DETAILED ANNOTATION TO OUR
PROPOSED PACKAGE INSERT. SPECIFICALLY, THE
ADVERSE EVENTS SECTION THAT INCLUDES REFERENCE
TO THE NUMBER OF PATIENTS STUDIED IN TOTAL AS
WELL AS VARIOUS SUBSETS. ALSO PROVIDE A GRAPHIC
DISPLAY OF THE DIFFERENCE BETWEEN BLOOD
PRESSURE MEASUREMENTSIN QUINAPRIL-TREATED
PATIENTS VERSUS PLACEBO-TREATED PATIENTS IN THE
24-HOUR BLOOD PRESSURE MONITORING STUDY (906-327)

06-DEC-90 26 LETTER RE: TELEPHONE CONVERSATION
CONTENT:

LETTER TO: ALI, MIRZA DR.
CI-906
RE: TELEPHONE CONVERSATION OF 26-NOV-90;
CLARIFICATION AS TO WHICH RATS IN THE
CARCINOGENICITY STUDY DIED DUE TO GAVAGE ERRORS.
NEW DATA DISKETTE ENCLOSED.

07-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRM MS. BONGIOVANNI'S TELEPHONE CALL
OF 06-DEC-90.
CONTACT PERSON: LIPICKY, RAY DR.
FDA MEETIN RE: IT WOULD NOT BE POSSIBLE FOR
DR. TEMPLE TO APPROVE THE NDA THIS MONTH. HE
PROJECTED "APPROVABLE" IN FEB/MAR AND "APPROVAL"
IN MAR/APR. HE RECOMMENDED OUR COMPLETING THE
SAFETY UPDATE NOW SO AS NOT TO EXTEND THE TIMING
BETWEEN APPROVABLE AND APPROVAL. DISCUSSION
OF THE MINIMUM ACCEPTABLE SAFETY UPDATE.

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07-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: DROP-OFF PATIENT INFORMATION BOOKLET FOR
REVUEW

CONTACT PERSON: PURVIS, WILLIAM

FDA MEETING RE: MR. PURVIS AGREED TO PASS ON THE
BOOKLET TO MR. FEATHER, BUT AT A SUPERFICIAL
FIRST GLANCE, THE BOOKLET DID NOT APPEAR TO BE A
PROBLEM.

07-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: OUTSTANDING ISSUES CONCERNING NDA REVIEW.
CONTACT PERSON: CHEN, SHAW DR.

RE: FDA MEETING WITH DR. MERINO, I. MARTIN, DR.
CHEN AND MS. BONGIOVANNI TO DISCUSS CONCERNS
WITH BIOMETRICS, PHARMACOLOGY, BIOPHARMACEUTICS,
LABELING, SAFETY UPDATE, DIVISIONAL REVIEW,
AND INSPECTION.

10-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: SBA QUESTION.

CONTACT PERSON: CHEN, SHAW DR.

TELEPHONE CONVERSATION RE: QUESTION ON NUMBERS OF
PATIENTS IN TWO TABLES OF THE SBA. QUESTION
CONCERNING THE PERCENTAGE OF PATIENTS WHO
WITHDREW. BOTH QUESTIONS WERE RESOLVED.

10-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF BIOPHARM. & BIOMETRICS REVIEWS.

CONTACT PERSON: BONGIOVANNE, KATHLEEN

TELEPHONE CONVERSATION RE: NOTHING NEW ON THE
STATUS OF THE BIOPHARM. OR BIOMETRICS REVIEWS
SINCE MEETING ON FRIDAY.

10-DEC-90
CONTENT:

27 LEETER RE: PROPOSED PACKAGE INSERT

LETTER TO: LIPICKY, RAYMOND, J., M.D.
CI-906

LETTER RE: REQUEST MADE ON 07-DEC-90 FOR UPDATED
ANNOTATION FOR THE DOSAGE AND ADMINISTRATION
SECTION OF THE PROPOSED PACKAGE INSERT. ENCLOSED
IS PROPOSED TEXT AND THE APPROPRIATE REFERENCE.

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11-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUESTION ON 906-327 CLINICAL REPORT
CONTACT PERSON: FRIEDMAN, BASIL, DR.
TELEPHONE CALL FROM FDA RE: REQUEST ADDITIONAL
INFORMATION REGARDING THE FINAL REPORT OF
906-327. PARKE-DAVIS RETURNED CALL AND WERE
ABLE TO ANSWER HIS QUESTIONS.

13-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: SAFETY UPDATE PROPOSAL
CONTACT PERSON: BONGIOVANNI, DATHLEEN
FDA MEETING RE: SAFETY UPDATE OUTLINE PROPOSAL
FOR OUR FINAL SAFETY UPDATE; THIS IS TO BE
DISCUSSED WITH DR. LIPICKY AND GET BACK TO US
NEXT WEEK.

14-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: REVIEW OF ACCUPRIL PATIENT INFORMATION
BOOKLET.
FDA CONTACT PERSON: FEATHER, KEN
FDA MEETING RE: CHANGES REQUESTED TO BOOKLET ON
PAGES 7 & 8; AND THAT "ACCUPRIL IS A UNIQUE BLOOD
PRESSURE MEDICATION" BE CHANGED TO "ADVERSE DRUG
REACTIONS ARE USUALLY MILD AND TRANSIENT".

14-DEC-90
CONTENT:

FDA CONTACT EMMO

MEMO RE: RECEIPT OF CI-955
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: FDA INFORMED US CI-955
NDA ARRIVED. DISCUSSED QUINAPRIL NDA REVIEW.
ALSO CONFIRMED THAT DR. CHEN IS COMMITTED TO
FINISHING HIS REVIEW AS SOON AS POSSIBLE.

19-DEC-90
CONTENT:

FDA CONTACT MEMO

MEMO RE: ADVISORY COMMITTEE NOTIFICATION
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO
TELEPHONE CONVERSATION RE: ALL SPONSORS OF
APPROVED AND PENDING NDAS FOR ACE INHIBITORS
INVITED TO CARDIO-RENAL ADVISORY COMMITTEE
TO BE HELD 18-JAN-91.

QUESTIONED IF BENAZEPRIL HAD BEEN APPROVED.

INFORMED OUR PROPOSAL FOR THE QUINAPRIL SAFETY
UPDATE WAS FINE.

THE NDA STILL HAS NOT LEFT THE DIVISION.

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20-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: FDA CONFERENCE DATE
CONTACT PERSON: FORGARTY, PAULINE
TELEPHONE CONVERSATION RE: OFFERED MEETING DATE
OF 24-JAN-91 TO DISCUSS THE INDICATIONS THAT
WERE FOUND APPROVABLE BY THE FDA. REQUESTED
HOLD ON DATE BUT WOULD PREFER TO HAVE A MEETING
IN EARLY FEBRUARY.

26-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: INVITE TO PRE-ADVISORY COMMITTEE MEETING
CONTACT PERSON: MCDONALD, ZELDA
TELEPHONE CALL FROM FDA RE: FDA'S INVITE TO
PRE-ADVISORY COMMITTEE MEETING TO DISCUSS EFFECTS
OF ANTIHYPERTENSIVE MEDICATIONS ON LEFT
VENTRICULAR HYPERTROPHY (LVH) ON 18-JAN-91.

26-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: ANOTHER QUESTION ON SBA
CONTACT PERSON: CHEN, SHAW, DR.
TELEPHONE CALL FROM FDA RE: TO CLARIFY TWO POINTS
IN THE SBA:
1) PAGE 219, REQUEST SUPPORTIVE INFORMATION ON
STATEMENT MADE IN THE FIRST TWO PARAGRAPHS.
2) HE HAS MET WITH DR. LIPICKY. EXPECTS THE
NDA TO BE AT DR. TEMPLE'S DESK EARLY NEXT
WEEK.

27-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUINAPRIL HYDROCHLORIDE
CONTACT PERSONS: WOLTERS, R., DR.
CUNNINGHAM, D., MS.
VISITED FDA RE: TO DISCUSS OUR LATEST EXPERIENCE
WITH THE COMPLIANCE DIVISION (NEWARK DISTRICT).
DISCUSSED THE FOLLOWING CHANGES TO BE SUBMITTED
AS AN NDA AMENDMENT:
1) REMOVAL OF THE 40MG TABLET FROM THE NDA.
2) CHANGE THE COMMERCIAL BATCH SIZES OF THE 5,
10 AND 20 MG TABLETS.
3) REPLACE THE ILLUSTRATIVE MASTER BATCH RECORDS
WITH THE COMMERCIAL MASTER BATCH RECORDS.
4) REVISE BULK CONTAINER LABELS TO SPECIFY LOW
HUMIDITY STORAGE.
FDA ALSO REQUESTED THE FOLLOWING:
1) COPY OF THE NOTICE OF ADVERSE FINDINGS LETTER.
2) TABLES COMPARING THE BATCH FORMULA STRENGTH.
3) COMPARISON OF MASTER BATCH RECORDS.
4) COPIES OF THE COMMERCIAL MASTER BATCH RECORDS.
5) ANALYTICAL DATA.

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27-DEC-90 FDA CONTACT PERSON
CONTENT:

MEMO RE: PROVIDE ANSWER TO QUESTION OF 26-DEC-90.
CONTACT PERSON: CHEN, SHAW
FDA MEETING RE: PROVIDED ATTACHED DOCUMENTATION
TO ANSWER QUESTIONS OF 26-DEC-90; AT REVIEW OF
MATERIALS CHANGES WERE REQUESTED (SEE MEMO).
DISCUSSION ALSO INCLUDED STATUS OF THE REST OF
THE NDA REVIEW.

27-DEC-90 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS CHECK
CONTACT PERSON: BONGIOVANNI, KATHLEEN
FDA MEETING RE: UPDATED WITH CONVERSATION WITH
DR. CHEN. DIVISIONAL RESPONSE TO BENAZEPRIL
PROMOTIONAL PIECE WAS THAT IT WAS PROBABLY OK,
EXCEPT QUESTIONED USE OF INDICATION FOR
HYPERTENSION OF THE STOCKING ANNOUNCEMENT.

28-DEC-90 28 LETTER RE: DRAFT SUMMARY BASIS OF APPROVAL
CONTENT: LETTER TO: LIPICKY, RAYMOND, J. M.D.
CI-906
RE: REQUESTED INFORMATION FOR DR. CHEN; ATTACHED
ARE TWO REPLACEMENT PAGES WHICH HAVE INCORPORATED
RESPONSES TO THESE QUESTIONS.

31-DEC-90 FDA CONTACT MEMO
CONTENT: MEMO RE: FINAL COMMENT ON NDA
CONTACT PERSON: CHEN, SHAW
TELEPHONE CONVERSATION RE: RECEIVED MATERIALS SENT
TO HIM; INFORMATION WAS FINE WITH ONE QUESTION.
QUESTION REGARDING 16 PATIENTS WITH NEUTROPHIL
COUNT <1500 AND DID NOT RETURN TO NORMAL ON
THERAPY IT IS POSSIBLE FOR THE NDA TO BE
OUT OF THE DIVISION BY THE END OF THE WEEK.

31-DEC-90 29 LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS
CONTENT: LETTER TO: LIPICKY, RAYMOND J., M.D.
VOL. 6.1
RE: TO AMEND THE CHEMISTRY, MANUFACTURING AND
CONTROLS SECTION OF THE NDA AS FOLLOWS:
1) COMMERCIAL BATCH FORMULAE FOR 5, 10 AND 20 MG
ACCUPRIL TABLETS.
2) COMPARISON OF NDA AND CURRENT MASTER BATCH
RECORDS FOR THE 10 MG TABLET.
3) CURRENT MASTER BATCH RECORDS FOR 5, 10 AND 20
MG ACCUPRIL TABLETS.
4) BULK CONTAINER LABELS.
5) STABILITY DATA.
6) NOTICE OF ADVERSE FINDINGS LETTER.

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02-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRM RECEIPT OF TELEFAX
CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: CONFIRMED RECEIPT OF
TELEFAX WITH ANSWERS OF QUESTION ON 31-DEC-90.
A REQUEST WAS ALSO MADE OF PATIENTS WITH
ABNORMAL NEUTROPHIL COUNTS THAT NORMALIZED;
INFORMATION WAS OBTAINED FROM DR. KNAPP.

03-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS CHECK
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: RECOMMENDATION THAT ANY
OUTSTANDING DOCUMENTATION BE SUBMITTED AS SOON AS
POSSIBLE SO THAT THE APPROVABLE LETTER WILL HAVE
ALL APPROPRIATE REFERENCES. THIS WAS AGREED.

03-JAN-91 30 LETTER RE: GENERAL CORRESPONDENCE
CONTENT:

LETTER TO: LIPICKY, RAYMOND, J. M.D.
CI-906
RE: REQUEST FOR ADDITIONAL INFORMATION FOR 16
PATIENTS EXPERIENCING NEUTROPENIA AT THE LAST
STUDY VISIT; TABLE WITH INFORMATION IS ENCLOSED.
WE ALSO CONFIRM THAT PATIENT #8 WAS NOT COUNTED
IN ABOVE INFORMATION.
ALSO PROVIDED INFORMATION OF 44 PATIENTS WHOSE
LOW NEUTROPHIL COUNTS RETURNED TO NORMAL HAD
COUNTS < 100 DURING THE STUDY.

04-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: REQUEST FOR NARRATIVE SUMMARIES
CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: NARRATIVES SUMMARIES
FOR NINE PATIENTS WITH WBC < 2000/MM3; FIFTEEN
PATIENTS WITH NEUTROPHIL COUNTS < 1000/MM3; AND
NINE PATIENTS WHOSE NEUTROPHIL COUNT WAS <
1000/MM3, THEN SUBSEQUENTLY RETURNED TO NORMAL;
ARE TO BE SENT AS SOON AS POSSIBLE.

08-JAN-91 31 LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS
CONTENT:

LETTER TO: LIPICKY, RAYMOND J. M.D.
CI-906
RE: OUR PENDING NDA (19-885) FOR ACCUPRIL TABLETS,
SUBMITTED ON 26-JAN-89 AND THE AMENDMENT TO THE
CHEMISTRY, MANUFACTURING AND CONTROLS SECTION OF
THE NDA DATED 31-DEC-90.

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08-JAN-91	32	LETTER RE: GENERAL CORRESPONDENCE
CONTENT:		LETTER TO: LIPICKY, RAYMOND J. M.D. CI-906 RE RESPONSE TO: FDA CONTACT MEMO DATED 04-JAN-91 FROM DR. CHEN; REQUESTED INFORMATION ENCLOSED.
09-JAN-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: DELIVER DESK COPIES OF NDA AMENDMENT CONTACT PERSON: WOLTERS, ROBERT FDA MEETING RE: DELIVERED DESK COPIES OF 2 AMENDMENTS (08-JAN-91 AND 31-DEC-90) TO THE QUINAPRIL NDA CMC SECTION. INFORMED DR. WOLTERS INSPECTION OF THE MOPS MANUFACTURING FACILITY BEGAN 08-JAN-91.
09-JAN-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: RESPONSE TO BENAZAPRIL PRE-APPROVAL AD CONTACT PERSON: CAVANAUGH, TOM TELEPHONE CONVERSATION RE: THE BENAZAPRIL ANNOUNCEMENT (FAX'ED TO FDA) WAS VIOLATIVE FOR A PRE-APPROVAL AD. FDA WOULD BE CONTACTING CIBA- GEIGY DIRECTLY TO DISCUSS THIS PROMOTIONAL ACTIVITY.
09-JAN-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: NDA STATUS CONTACT PERSON: BONGIOVANNI, KATHLEEN FDA MEETING RE: DELIVERED DESK COPY OF THE NARRATIVES REQUESTED BY DR. CHEN THAT WERE SUBMITTED TO THE NDA. FDA INFORMED THAT 1) BIOMETRICS REVIEW IS FINALIZED AND SIGNED 2) DR. LIPICKY WOULD NOT WAIT FOR BIOPHARM. REVIEW WHICH IS STILL OUTSTANDING. 3) DR. LIPICKY IS STILL DOING SECONDARY REVIEW OF PHARMACOLOGY. INFORMED FDA THE CMC NDA AMENDMENTS; THEIR RATIONALE AND OF THE ONGOING MOPS SITE INSPECTION
09-JAN-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: CONFIRM 18-JAN-91 ATTENDANCE CONTACT PERSON: MCDONALD, ZELDA FDA MEETING RE: CONFIRMED THAT P-D WOULD BE ATTENDING THE 18-JAN-91 PM MEETING ON LV HYPERTROPHY AND ANTIHYPERTENSIVES. 5 WILL BE IN ATTENDANCE.

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10-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO 09-JAN-91 VISIT
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: CONVERSATION WITH
MR. CAVANAUGH WHO INFORMED US HE FELT THE
BENAZAPRIL AD WAS VIOLATIVE.
REQUESTED MEETING WITH DR. LIPICKY, MARTIN AND
MERINO NEXT WEEK.

14-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRM MEETING
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: CONFIRMED MEETING WITH
DRS. LIPICKY, CHEN, MARTIN, AND MERINO ON 18-JAN
AT 8:45 AM.

18-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: INFORM RESULTS OF SITE INSPECTION.
CONTACT PERSON: WOLTERS, ROBERT
FDA MEETING RE: INSPECTION OF MOPS FOR QUINAPRIL
WENT WELL AND A 483 WAS NOT ISSUED.

18-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUINAPRIL NDA ISSUES.
CONTACT PERSON: BONGIOVANNI, KATHLEEN
FDA MEETING RE: MOPS INSPECTION WENT WELL AND A
483 WAS NOT ISSUED.
REQUESTED NEW CLASS LABELING FOR ACE INHIBITORS
FOR USE IN PREGNANCY; SHE WILL SEND COPY WHEN
FINALIZED.
NEW MEDICAL REVIEWER ASSIGNED TO QUINAPRIL;
DR. SOMANI.

18-JAN-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS OF NDA REVIEW.
CONTACT PERSON: LIPICKY, RAY DR.
FDA MEETING RE: DISCUSSION OF STATUS OF NDA REVIEW
IN THE CARDIO-RENAL DIVISION.
MEETING HELD WITH DRS. MERINO, MARTIN, LIPICKY,
CHEN AND MS. BONGIOVANNI; SEE MEMO FOR DISCUSSION

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CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP ON DR. SOMANI'S REQUEST.
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: DISCUSSION OF HOW WE
WILL BE ANSWERING DR. SOMANI'S REQUEST FOR
INFORMATION.
FAX TO BE SENT TO US ON 24-JAN ABOUT SPONSORS FOR
THE ACE ADVISORY COMMITTEE; WE ARE TO RESPOND BY
25-JAN.
SHE IS TO CHECK WITH DR. FENICHEL ABOUT CHANGES
IN ACE PREGNANCY BOILERPLATE. IF NONE WILL FAX
CURRENT LABELING.
DISCUSSED OPTIONS OF SPEEDING UP DR. VANARSDALE'S
PHARMACOLOGY REVIEW.

24-JAN-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: AVAILABILITY OF INFORMATION ON ADVISORY
COMMITTEE.
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: FDA FAX'ED TO US;
-LATEST APPROVED PREGNANCY WORDING FOR VASOTEC
(FURTHER CHANGES MAY OCCUR)
-PROPOSED LIST OF QUESTIONS FOR CARDIO-RENAL
ADVISORY COMMITTEE MEETING ON ACE INHIBITORS
DOCUMENTS ARE ATTACHED

25-JAN-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM ADVISORY COMMITTEE PARTICIPATION
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO
TELEPHONE CONVERSATION RE: TO INFORM FDA THAT
PARKE-DAVIS WILL PARTICIPATE IN THE ACE
ADVISORY COMMITTEE AND ARE WILLING TO PRESENT
UNMASKED DATA ON QUINAPRIL.

29-JAN-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM ATTENDANCE AT FEBRUARY 20 PRE-
ADVISORY COMMITTEE MEETING
CONTACT PERSON: BONGIOVANNI, KATHLEEN, CSO
TELEPHONE CONVERSATION RE: CONFIRMING PARKE-DAVIS
ATTENDANCE TO 20-FEB-91 PRE-ADVISORY COMMITTEE
MEETING AND ACTUAL MEETING TO BE HELD ON
JUNE 6-7, 1991.

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01-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: INFORM OF GLP INSPECTION
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: INFORMED HER OF ONGOING
GLP INSPECTION OF THE QUINAPRIL RAT CARCINOGEN-
ICITY STUDY; SHE WAS NOT AWARE OF THIS.
ALSO INFORMED HER THAT DR. MERINO HAS BEEN IN
TOUCH WITH MARY DOUG TYSON AND DR. WEISSINGER
CONCERNING DR. VANARSDALE.

04-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: INFORM RESULTS OF PRE-CLINICAL INSPECTION
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: INSPECTION OF THE RAT
CARCINOGENICITY STUDY WAS COMPLETE AND NO -483
WILL BE ISSUED. DR. VANARSDALE REQUESTED THIS
INSPECTION IN SEP-90. INSPECTORS FOUND NOTHING
OF SIGNIFICANCE AND WILL CALL DR. VANARSDALE
WITH THEIR FINDINGS.

05-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: INFORM OF CLINICAL SITE INSPECTION AND
ASK FOR RAMAPRIL LABELING.
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: DR. MITCHELL OF
ALBUQUERQUE, NM, 906-238-5 HAS RECEIVED
NOTIFICATION BY THE FDA HOUSTON OFFICE OF
INSPECTION OF HIS SITE THIS WEEK.
CONFIRMED THE APPROVAL OF RAMAPRIL, APPROVAL
LETTER AND APPROVED LABELING WILL BE SENT.

05-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: TO DISCUSS THE STATUS OF THE PHARMACOLOGY
REVIEW FOR THE QUINAPRIL NDA.
CONTACT PERSON: WEISSINGER, JUDI
MEETING RE: FOLLOW-UP ON STATUS OF PHARMACOLOGY
REVIEW FOR QUINAPRIL NDA. SHE WILL FOLLOW-UP WITH
THE CARDIORENAL DIVISION TODAY. REVIEWED THE
HISTORY AS WELL AS RECENT GLP INSPECTION
REGARDING QUINAPRIL.

05-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUINAPRIL PHARMACOLOGY REVIEW
CONTACT PERSON: WEISSINGER, JUDI
TELEPHONE CONVERSATION RE: SHE HAD VISITED
CARDIORENAL DIVISION AND FOUND THE QUINAPRIL
PHARMACOLOGY/TOXICOLOGY REVIEW HAS BEEN TOP
PRIORITY SINCE OCT-89. SHE AGREED THAT THE REVIEW
TIME WAS TOO LONG AND WILL FOLLOW-UP WITH DR.
VANARSDALE DIRECTLY. CONFIRMED THAT THE BIOASSAY

WAS CLEAN, WILL FOLLOW-UP TO DETERMINE IF THEIR
ARE ANY SCIENTIFIC ISSUES. SHE WILL DO HER BEST
TO GET REVIEW COMPLETED.

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06-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO INFORMATION ON CLINICAL INVESTIGATIONS.
CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: SIX CLINICAL INVESTIGATORS WERE CHOSEN FOR INSPECTION (SEE MEMO).
ALSO DISCUSSED STRATEGIES FOR SUBMISSION OF THE FINAL SAFETY UPDATE.

06-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: RAMIPRIL
CONTACT PERSON: BONGIOVANNI, KATHLEEN
MAIL SENT RE: RAMIPRIL APPROVAL LETTER AND PACKAGE INSERT FOR USE IN PREPARING ACCUPRIL LABELING.

06-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTIONS ON NDA AMENDMENTS.
CONTACT PERSON: SAMARA, EMIL DR.
TELEPHONE CONVERSATION RE: REVIEW OF NDA COMPLETED; CURRENTLY REVIEWING OUR RECENT AMENDMENTS, HE HAD 4 MINOR QUESTIONS.
QUESTION 1 WAS ANSWERED IMMEDIATELY, QUESTIONS 2-4 WERE ANSWERED IN A RETURN CALL ON 07-FEB.
SEE MEMO FOR QUESTIONS AND ANSWERS.
STILL HAS CONCERNS WITH THE VALIDATION OF THE ANALYTICAL METHODOLOGY. SPECIFIC CONCERNS REVOLVED AROUND THE THREE METHODS HE REVIEWED.
SEE MEMO FOR THOSE CONCERNS.
RECOMMENDED WE WAIT UNTIL WE RECEIVE DEFICIENCY LETTER AND THEN REPLY.

06-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTIONS ON NDA AMENDMENTS
CONTACT PERSON: SAMARA, EMIL, DR.
TELEPHONE CALL FROM FDA RE: REQUEST THE FOLLOWING INFORMATION:
1) DEFINITION OF OUR USE OF THE TERM "MARKET-IMAGE".
2) FORMULATIONS USED IN STUDIES 906-342, -305, -328 WHICH WERE SUBMITTED TO THE NDA ON 7/25/90.
3) REASON FOR SUBMISSION OF REPORT ON STUDY 906-81 IN SUBMISSION OF 10/31/90.
4) SITE FOR ANALYTICAL METHODS IN ABOVE STUDIES.

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11-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: NDA STATUS
CONTACT PERSON: BONGIOVANNI, KATHLEEN
MEETING RE: DR. VANARSDDEL, PHARMACOLOGY REVIEW
REMAINS OUTSTANDING.
LOOKING FOR 20-FEB SUBMISSION TO ANSWER DR.
SAMARA QUESTIONS. THIS IS ALSO THE DATE PLANNED
TO SUBMIT THE FINAL SAFETY UPDATE AND REVISED
DRAFT LABELING TO NDA.
CONFIRMED MEETING TO DISCUSS THE ACE ADV. CMTE.
WILL BE 20-FEB AT 10:00 AM IN ROOM 16A29.

12-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTION ON CARCINOGENICITY DATA
CONTACT PERSON: VANARSDDEL, WILLIAM DR.
TELEPHONE CONVERSATION RE: DR. RESNICK IS
REVIEWING STATISTICIAN'S REVIEW OF QUINAPRIL RAT
AND MOUSE CARCINOGENICITY STUDIES. THE HISTORICAL
DATA ON TUMOR INCIDENCES IN OUR CONTROL GROUPS OF
RATS AND MICE CAN NOT BE LOCATED. WILL FIND OUT
AND GET BACK TO HIM.
ASKED HIS STATUS ON THE REST OF THE REVIEW; HE IS
WORKING ON IT.

14-FEB-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO DR. VANARSDDEL'S REQUEST FOR
"HISTORICAL CONTROLS" FOR RAT
CARCINOGENICITY STUDY.
CONTACT PERSON: RESNICK, CHARLES PH.D.
TELEPHONE CONVERSATION RE: TO CLARIFY REQUEST FOR
HISTORICAL CONTROL INFORMATION FROM DR. VANARSDDEL
BASED ON RECENTLY COMPLETED STATISTICAL REVIEW OF
THE CARCINOGENICITY STUDIES ISSUES NEED TO BE
ADDRESSED. STATISTICAL ANALYSIS NOTED A TREND
WITH DOSE IN FEMALE RATS (SEE MEMO FOR LISTED
TUMORS). BECAUSE OF THE FINDING IN THE REVIEW A
REQUEST WAS MADE TO PROVIDE HISTORICAL CONTROL
INFORMATION (SEE MEMO FOR INFORMATION). DR.
RESNICK WOULD LIKE TO PUT THIS ISSUE TO REST AS
SOON AS POSSIBLE. THIS COULD BE CRITICAL PATH TO
APPROVAL, NEED FOR QUICK TURNAROUND.

19-FEB-91 33 SAFTEY UPDATE
CONTENT:
VOLUMES = 14

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19-FEB-91	34	LETTER RE: ANALYTICAL METHODOLOGIES
CONTENT:		<p>LETTER TO: LIPICKY, RAYMOND J. M.D. CI-906 RE RESPONSE TO QUESTIONS FROM DR. SAMARA PER TELEPHONE CONVERSATION ON 07-FEB: INFORMATION ON ANALYTICAL METHODOLOGIES</p> <ol style="list-style-type: none">1) 4192-00292, HPLC, FRIEBURG VALIDATION ON STABILITY IN SHIPPING AND RECOVERY METHOD. LIST OF CLINICAL STUDIES WHICH UTILIZED THIS METHOD.2) 764-00441, GC FOR HYMAN PLASMA SITE WHERE VALIDATION WAS PERFORMED. BLANK CHROMATOGRAM. VALIDATION ON RECOVERY/STABILITY LIST OF CLINICAL STUDIES WHICH UTILIZED THIS METHOD.3) 764-01083, GC FOR HUMAN URINE VALIDATION ON RECOVERY/STABILITY. BLANK CHROMATOGRAM. LIST OF CLINICAL STUDIES WHICH UTILIZED THIS METHOD. <p>REQUESTED INFORMATION ATTACHED, EXCEPT FOR BLANK CHROMATOGRAPHS, PROVIDED IN 1-2 WEEKS.</p>
20-FEB-91		FDA CONTACT MEMO
CONTENT:		<p>MEMO RE: FOLLOW-UP TO REQUEST FOR HISTORICAL CONTROLS FROM RAT CARCINOGENICITY STUDY. CONTACT PERSON: RESNICK, CHARLES PH.D MEETING RE: TO CLARIFY HIS REQUEST FOR "MEAN SURVIVAL TIME" IN HISTORICAL VS. CONCURRENT CONTROLS. WE QUESTIONED STATUS OF DR. VAN ARSDEL'S REVIEW. END OF FEBRUARY COULD BE POSSIBLE FOR COMPLETION OF REVIEW.</p>
20-FEB-91		FDA CONTACT MEMO
CONTENT:		<p>MEMO RE: DELIVERY OF DESK COPIES CONTACT PERSON: BONGIOVANNI, K. MEETING RE: MET AND DISCUSSED FOLLOWING:</p> <ol style="list-style-type: none">1 DELIVERED 2 DESK COPIES OF THIRD SAFETY UPDATE.2 DELIVERED 2 DESK COPIES OF RESPONSE TO ASSAY VALIDATION QUESTIONS FROM BIOPHARMACEUTICS.3 BRIEFLY OUTLINED REQUEST FOR HISTORICAL CONTROLS FROM PHARMACOLOGY/TOXICOLOGY REVIEWER.4 INDICATED THAT WE WOULD PROVIDE THE REQUESTED OVERVIEW OF THE CHF SUBMISSION AND IND LOCATION OF CHF PROTOCOLS EARLY NEXT WEEK. WE DID NOT INTEND TO PURSUE ANY ADDITIONAL INDICATION AT THIS TIME.5 REGARDING QUIET STUDY; WE WOULD OPEN SEPARATE IND FOR PATIENT POPULATION, AND REQUEST REVIEW OF PROPOSED PROTOCOL.6 NO SPECIFIC UPDATE OF THE STATUS OF DR. VAN ARSDEL'S TOXICOLOGY REVIEW.

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20-FEB-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: PRE-ADVISORY COMMITTEE PLANNING MEETING -
ACE INHIBITORS
CONTACT PERSON: LIPICKY, RAYMOND DR.
MEETING RE: MEETING OPENED WITH SUMMARY OF MOST
RECENT TELEFAX (ATTACHED) HIGHLIGHTING FDA'S
CHANGING AGENDA CONCERNING ACE INHIBITORS.
ATTENDEES ASKED FOR MORE SPECIFICS ON REQUESTED
DATA AND QUESTIONS TO BE ADDRESSED.
SEE MEMO FOR LIST OF ISSUES DISCUSSED.

25-FEB-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: TABLET EXPIRATION DATING
CONTACT PERSON: CUNNINGHAM, D. MS.
TELEPHONE CONVERSATION RE: SHE HAD COMPLETED HER
REVIEW AO AMENDMENT AND HAD NO QUESTIONS. SHE
ALSO STATED OUR REQUEST FOR 36-MONTH
EXPIRATION ON TABLET WAS APPROVED.
BRENNAN IS TO CONTACT COMPLIANCE DISTRICT OFFICE
TO CONFIRM RECOMMENDATION FOR APPROVAL WAS
FORWARDED TO WASHINGTON COMPLIANCE OFFICE AS SHE
HAS NOT RECIEVED INSPECTION REPORT.

25-FEB-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO QUESTIONS ON NDA AMENDMENTS
CONTACT PERSON: SAMARA, EMIL DR.
TELEPHONE CONVERSATION RE: STILL NEEDS ADDITIONAL
INFORMATION ON RECOVERY, NOT NECESSARILY
ABSOLUTE RECOVERY.
WE SHOULD WAIT RO RECEIVE LETTER FROM DIVISION
BEFORE RESPONDING FURTHER, ISSUES WOULD NOT HOLD
UP APPROVAL.

25-FEB-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: COMMENT ON SBA
CONTACT PERSON: CHEN, SHAW DR.
MEETING RE: HE MIGHT ASK US TO AGAIN UPDATE THE
QUINAPRIL SBA, HE COULD FAX US THE PAGES HE
WANTED CHANGED AS THIS WOULD NOT BE A PROBLEM.

25-FEB-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: MISCELLANEOUS TOPICS
CONTACT PERSON: BONGIOVANNI, KATHLEEN
MEETING RE: PROMISED TO CALL WHEN SHE RECEIVED
DR. SAMARA'S RESPONSE TO OUR RECENT SUBMISSION.
OUR RESPONSE TO DR. RESNICK'S REQUEST WOULD BE
TO THEM ON 26-FEB.
DISCUSSION OF NEXT PRE-MEETING FOR CARDIO-RENAL
ADVISORY COMMITTEE.

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25-FEB-91	35	LETTER RE: STATISTICAL ANALYSIS: PHARMACOLOGY
CONTENT:		LETTER TO: LIPICKY, RAYMOND J. M.D. CI-906 RE RESPONSE TO 14-FEB-91 REQUEST: ATTACHMENT TO THIS LETTER, WE HAVE PROVIDED THE HISTORICAL CONTROL INFORMATION IN FEMALE RATS AS REQUESTED.
28-FEB-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: NEXT MEETING OF PRE-ADVISORY COMMITTEE PLANNING GROUP. CONTACT PERSON: BONGIOVANNI, KATHLEEN FAX RE: MATERIALS PROMISED TO BE SENT TO US LAST WEEK WILL BE SENT BY FAX TOMORROW. NEXT PLANNING MEETING SCHEDULED FOR 20-MAR-91, AT 1:00 PM IN 13B39.
28-FEB-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF QUINAPRIL REVIEW CONTACT PERSON: RESNICK, CHARLES DR. TELEPHONE CONVERSATION RE: CONFIRMED RECEIPT OF RECENT SUBMISSION IN RESPONSE TO HIS QUESTION ON HISTORICAL CONTROLS IN CARCINOGENICITY STUDIES. ALSO ALERTED US TO ANOTHER POSSIBLE CONCERN, REGARDING HIGHER DOSE LEVELS USED IN THESE STUDIES (SEE MEMO). CONFIRMED THAT DR. VANARSDEL WILL NOT BE THROUGH WITH HIS REVIEW IN FEBRUARY. AGREED MARTIN CAN STOP TO CHECK NEXT WEEK ON HIS ESTIMATE OF THE COMPLETION OF THE DRAFT PHARMACOLOGY REVIEW. PASSED ON FOR HIS INFORMATION ONLY THAT DRS. MERINO AND CRESSWELL WILL BE WITH DRS. PECK AND TEMPLE ON 01-MAR AND LIKELY THEIR CONCERN WOULD BE RAISED OVER PHARMACOLOGY REVIEW.
28-FEB-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: REQUESTS FROM THIRD SAFETY UPDATE. CONTACT PERSON: CHEN, SHAW DR. TELEPHONE CONVERSATION RE: REQUEST FOR FOLLOWING TABLE TO HELP HIS REVIEW OF 20-FEB SUBMISSION OF THIRD SAFETY UPDATE. FROM PLACEBO CONTROLLED STUDIES, PROVIDE RATE (PERCENT) - WITHDRAWALS DUE TO AES - NON-FATAL, SERIOUS EVENTS - DEATHS - TOTAL ADVERSE EVENTS SEE MEMO FOR COMPLETE REQUEST FOR INFORMATION. HE MIGHT HAVE SUGGESTED CHANGES TO THE SBA READY NEXT WEEK. WISHED TO KNOW WHY 7 DEATHS ARE LISTED FOR QUINAPRIL FROM CONTROLLED STUDIES IN THE SAFETY

UPDATE, SBA LISTS 9 QUINAPRIL DEATHS.

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01-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO 28-FEB REQUEST.
CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: REQUEST DATA FOR
PATIENTS WITHDRAWING, DYING, SUFFERING A SERIOUS
AE OR SUFFERING ANY AE. HE WOULD NOW LIKE THESE
PERCENTAGES FOR ALL QUINAPRIL PATIENTS. THESE
DATA MAY AGAIN BE BROKEN DOWN BY HYPERTENSION
AND CHF.

01-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: DELAY IN PHARMACOLOGY REVIEW.
CONTACT PERSON: TEMPLE, DR.
MEETING RE: DISCUSSION OF DR. VAN ARSDALE DELAY IN
THE PHARMACOLOGY REVIEW. MENTIONED WE WOULD
APPRECIATE HIS RAPID REVIEW OF THE NDA WHEN
RECEIVED. HE WILL LOOK INTO THE MATTER.

04-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRM ATTENDANCE AT 20-MAR ACE
INHIBITOR MEETING/QUIET PROTOCOL
SUBMISSION.
CONTACT PERSON: BONGIOVANNI, K. MS.
TELEPHONE CONVERSATION RE: TO CONFIRM OUR
ATTENDANCE AT NEXT PLANNING MEETING TO BE HELD
20-MAR-91 AT 1:00 PM IN 13B39 AT THE PARKLAWN
BUILDING.
INDICATED SUBMITTING THE DRAFT QUIET STUDY
PROTOCOL FOR REVIEW, WOULD LIKE TO MEET WITH
DR. LIPICKY TO DISCUSS STUDY. SHE WILL CHECK ON
POSSIBLE DATES. BOTH AGREED WE COULD SEND NEW
PROTOCOL TO EXISTING IND WITH UNDERSTANDING THAT
WE WOULD OPEN SEPARATE IND WHEN PROTOCOL WAS
FINALIZED.

04-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: AGENDA FOR NEXT MEETING ON ACE INHIBITORS
CONTACT PERSON: LIPICKY, RAYMOND
TELEPHONE (FAX) RE: SEE ATTACHED COMMUNICATION
REGARDING UPCOMING ACE INHIBITOR MEETING,
INCLUDING DATE OF THE NEXT WORK GROUP MEETING
(20-MAR, 1:00 PM, 13B39).

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04-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO EARLIER DISCUSSION
CONTACT PERSON: RESNICK, CHARLES
MEETING RE: FDA SUGGESTED WE SUBMIT THE ATTACHED
INTERNAL MEMO REGARDING COMPARATIVE ANIMAL-HUMAN
SERUM LEVELS, TO THE NDA. SUGGESTED HOW OUR
RESPONSE SHOULD NOTE, (SEE MEMO).
TO CHECK BACK WITH HIM ON WEDNESDAY TO DISCOVER
THE OUTCOME OF MEETING WITH DR. VAN ARSDEL.

04-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA
CONTACT PERSON: BONJIOVANNI, KATHLEEN
MEETING RE: HAS HEARD NOTHING OF DR. VAN ARSDEL'S
REVIEW.
PROVIDED HER DESK COPY OF 3/4 AMENDMENT TO THE 3RD
SAFETY UPDATE REQUESTED BY CHEN.
BRIEFLY DISCUSSED HER FAX ON 01-MAR OF THE ACE
ADVISORY COMMITTEE MEETING.

04-MAR-91
CONTENT:

36 LETTER RE: SAFETY UPDATE

LETTER TO: LIPICKY, RAYMOND M.D.
CI-906
RE: RESPONSE TO REQUEST FROM DR. CHEN ON 28-FEB
AND 01-MAR. ENCLOSED ARE ATTACHMENTS OF REQUESTED
INFORMATION.

05-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: CLARIFICATION OF DATA IN FINAL SAFETY
UPDATE.
CONTACT PERSON: FRIEDMAN, BASIL DR.
TELEPHONE CONVERSATION RE: FRIEDMAN CALLED TO ASK.
1) ON P.171 OF THE UPDATE DOES THE COLUMN HEADED
"QUINAPRIL" INCLUDE DIURETIC TREATED PATIENTS?
2) ON P.174, WHAT DOES PROT A1 AND PROT B MEAN?

CONFERING WITH LLOYD KNAPP, RETUNED CALL TO ANSWER
HIS QUESTIONS.

05-MAR-91
CONTENT:

37 LETTER RE: PLASMA CONCENTRATIONS

LETTER TO: LIPICKY, RAYMOND M.D.
CI-906
RE: AVAILABILITY OF INFORMATION ON THE PLASMA
CONCENTRATIONS OBTAINED IN THE RAT AND MOUSE
CARCINOGENICITY STUDIES.

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06-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO RESPONSE TO SAFETY UPDATE CONTACT PERSON: CHEN, SHAW M.D. MEETING RE: CONFIRMED HIS RECEIPT OF DISK COPY OF OUR 04-MAR SUBMISSION; OFFERED TO PICK UP ANY CHANGES TO THE SBA HE WOULD LIKE MADE. HE WOULD LIKE AN EXPLANATION OF APPARENT INCONSISTENCY OF THE THIRD SAFETY UPDATE AND THE SBA REGARDING TOTAL DEATHS. WE SHOULD BE PREPARED TO DEFEND; DURING LABELING; THAT OUR FOOD INTERACTION STUDY WAS CONDUCTED WITH A NON-FDA STANDARD MEAL.
07-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA CONTACT PERSON: RESNICK, CHARLES MEETING RE: DR. VANARSDEL'S COMPLETION OF THE DRAFT OF PHARMACOLOGY REVIEW BY 15-MAR.
08-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: ADDITIONAL SAFETY UPDATE QUESTIONS. CONTACT PERSON: CHEN, SHAW DR. MEETING RE: HE HAS REVIEWED HIS SECONDARY REVIEW WITH DR. LIPICKY. THREE AREAS SHOULD BE ADDRESSED PRIOR TO THE NDA'S TRIP TO DR. TEMPLE: GOUT, RENAL FUNCTION, AND DR. FRIEDMAN'S REVIEW, SEE MEMO FOR COMPLETE DISCUSSION.
11-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: QUESTIONS ON 3RD SAFETY UPDATE. CONTACT PERSON: CHEN, SHAW TELEPHONE CONVERSATION RE: ANOTHER ERROR IN THE QUINAPRIL THIRD SAFETY UPDATE, SEE MEMO
12-MAR-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: REQUEST FOR ADDITIONAL SAFETY TABLE CONTACT PERSON: CHEN, SHAW DR. TELEPHONE CONVERSATION RE: REQUEST THAT WE PROVIDE ADDITIONAL INFORMATION IN REGARDS TO ADVERSE EVENTS. SEE MEMO

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13-MAR-91
CONTENT: FDA CONTACT MEMO

MEMO RE: QUESTION ON SAFETY UPDATE/SBA
CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: QUESTION ON THE SAFETY
UPDATE LABORATORY VALUE SHIFT TABLE; WHICH WAS
ANSWERED.
REQUESTED UPDATE TO SBA APPENDIX B.4 SUBMITTED TO
THE NDA ON 08-JAN-91. SHOULD BE UPDATED THROUGH
THE THIRD SAFETY UPDATE.

13-MAR-91
CONTENT: 38 LETTER RE: GENERAL CORRESPONDENCE

LETTER TO: LIPICKY, RAYMOND M.D.
CI-906
RE: REPONDING TO QUESTIONS RECEIVED ON 06-MAR,
08-MAR AND 12-MAR-91 CONCERNING OUR PENDING NDA

14-MAR-91
CONTENT: FDA CONTACT MEMO

MEMO RE: FOLLOW-UP ON STATUS OF PHARMACOLOGY
REVIEW.
CONTACT PERSON: RESNICK, CHARLES
MEETING RE: 15/MAR STILL REALISTIC FOR DR.
VANARSDEL'S COMPLETION OF THE DRAFT PHARMACOLOGY
REVIEW. HIS REVIEW OF THE STUDIES IS COMPLETE,
CURRENTLY COMPLETING WRITTEN REVIEW.
QUINAPRIL LISTED OUT OF THE DIVISION IN MARCH.

15-MAR-91
CONTENT: FDA CONTACT MEMO

MEMO RE: STATUS OF PHARMACOLOGY REVIEW
CONTACT PERSON: BONGIOVANNI, K. MS.
MEETING RE: CHECK ON STATUS OF DR. VAN ARSKEL'S
PHARMACOLOGY REVIEW, SHE HAD NOT RECEIVED, WILL
CHECK ON STATUS AND CALL.

18-MAR-91
CONTENT: FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO PHARMACOLOGY
CONTACT PERSON: BONGIOVANNI, DATHLEEN
TELEPHONE CONVERSATION RE: AT 1 PM MS. BONGIOVANNI
STILL HAD NOT RECIEVED THE PHARMACOLOGY REVIEW;
BUT PROMISED TO CALL WHEN IT ARRIVED.

18-MAR-91
CONTENT: FDA CONTACT MEMO

MEMO RE: QUESTION ON 13-MAR RESPONSE TO HIS
EARLIER QUESTIONS.
CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: WOULD LIKE DISCREPANCY
IN THE THIRD SAFTEY UPDATE (APPENDIX 8.7)
CLARIFIED.

LABORATORY ABNORMALITIES INCLUDED BOTH HYPOKALEMIA
AND DECREASED POTASSIUM; IS THIS CORRECT?
DRS. KNAPP AND MARTIN CLARIFIED DISCREPANCIES.
SCHEDULED MEETING ON WEDNESDAY 20-MAR AT 9:30 AM
TO DISCUSS UPDATE TO SBA APPENDIX B.4 AND MERGING
OF RELATED AE TERMINOLOGY.

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19-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTION FROM BIOPHARMACEUTICS REVIEW.
CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: LIKE TO KNOW IF ANY
DATA WERE AVAILABLE ON EFFICACY IN HEPATICLY
IMPAIRED PATIENTS.
DURING MEETING ON 20-MAR HE WAS PROVIDED WITH THE
ATTACHED PAGES FROM A RESEARCH REPORT IN THE NDA.
INFORMED THAT B/P DATA ARE NOT AVAILABLE.

19-MAR-91 39 LETTER RE: GENERAL CORRESPONDENCE
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
CI-906
RE: RESPONDING TO QUESTIONS RECIEVED ON 11-MAR,
18-MAR NAD 19-MAR; AND THE SAFTEY UPDATE
SUBMITTED 19-FEB-91. QUESTIONS WERE FROM
DR. SHAW CHEN.

20-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: REVIEW RESPONSES TO VARIOUS RECENT
REQUESTS.
CONTACT PERSON: CHEN, SHAW DR.
MEETING RE: UPDATE DRS. KNAPP AND CHEN ON OUR
RESPONSE TO RECENT QUESTIONS, ALL SATISFIED.
REVIEWED REQUEST TO COLLAPSE VARIOUS AE TERMS TO
PROVIDE A TRUER PICTURE OF THE AE PROFILE OF
QUINAPRIL. AGREED PRIORITY SHOULD BE THE AE
LISTING FROM CONTROLLED CLINICAL TRIALS,
ESPECIALLY IF IMPACTS LABELING.
DR. CHEN HAD NOT RECEIVED DRAFT PHARMACOLOGY
REVIEW FROM DR. VANARSDEL.
DR. CHEN RECEIVED BIOPHARMACEUTICS FINAL REVIEW.
PROVIDED US WITH COMMENTS AND LABELING SECTIONS
OF THE REVIEW (ATTACHED).

20-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS OF VANARSDEL REVIEW.
CONTACT PERSON: RESNICK, CHARLES
MEETING RE: STILL WAITING FOR DR. VANARSDEL
PHARMACOLOGY REVIEW.

20-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: NDA STATUS
CONTACT PERSON: BONGIOVANNI, KATHLEEN
MEETING RE: NO NEW INFORMATION ON THE PHARMACOLOGY
REVIEW. CONFIRMED THAT BENAZAPRIL WAS NOT YET
APPROVED.

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21-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO 20-MAR MEETING ON ACE
ADVISORY COMMITTEE.

CONTACT PERSON: BONGIOVANNI, KATHLEEN
TELEPHONE CONVERSATION RE: CONFIRM OUR PSEUDONYM
FOR QUINAPRIL TO BE USED DURING THE ADVISORY
COMMITTEE PRESENTATION. AGREED ON "BESTAPRIL".
ALSO REQUESTED A CONTACT FOR PMA CONCERNING THE
COST OF CONSULTANTS.
NEXT MEETING OF GROUP WILL BE 19-APR AT 9 AM.

22-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO QUESTION ON WBC/NEUTROPHIL
COUNTS - THIRD SAFETY UPDATE.

CONTACT PERSON: CHEN, SHAW M.D.
TELEPHONE CONVERSATION RE: REQUEST THAT A
DENOMINATOR BE PROVIDED SO THAT HE COULD
CALCULATE THE INCIDENCE OF LOW WBC AND NEUTROPHIL
COUNTS. WE WILL PROVIDE THE EXACT NUMBER EARLY
NEXT WEEK. WE PROVIDED AN ESTIMATE UNTIL THAT
TIME.
NOTED THE DISCREPANCY IN SBA AND THE THIRD SAFETY
UPDATE RESULTED FROM INCLUDING CONTROLLED AND
UNCONTROLLED STUDIES IN THE FORMER, AND ONLY
CONTROLLED STUDIES IN THE LATTER.

22-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUESTION ON 19-MAR SUBMISSION IN RESPONSE
TO EARLIER QUESTION.

CONTACT PERSON: CHEN, SHAW DR.
TELEPHONE CONVERSATION RE: LABORATORY MEASUREMENTS
IN THE THIRD SAFETY UPDATE VARIED. WHY IS LATER
NUMBER LOWER?
REQUESTED DENOMINATOR TO USE TO CALCULATE THE NEW
INCIDENCE FIGURES FOR NEUTROPENIA AND DECREASED
WBC.

25-MAR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: QUINAPRIL NDA
CONTACT PERSON: TEMPLE, ROBERT DR.
TELEPHONE CONVERSATION RE: DR. VAN ARSDALE HAD
COMPLETED THE PHARMACOLOGY REVIEW AND WAS
DISCUSSING IT WITH HIS SUPERVISOR, DR. RESNICK.
DR. LIPICKY WOULD HAVE IT SHORTLY.

DR. TEMPLE'S REVIEW SHOULD NOT BE LONG AND SHOULD
NOT BE ANY PROBLEM.

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26-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: CHECK STATUS OF PHARMACOLOGY REVIEW.
CONTACT PERSON: BONGIOVANNI, K.
TELEPHONE CONVERSATION RE: CHECK OF STATUS OF
PHARMACOLOGY REVIEW; NO NEWS TO PROVIDE, BUT WILL
CALL AS SOON AS SHE RECEIVED THE REVIEW.
MEETING WITH DR. LIPICKY REGARDING THE QUIET
PROTOCOL, DATE OF 12-APR AT 9:30 AM HAS BEEN
PROPOSED. WILL CONFIRM THIS DATE WITH P-D
REPRESENTATIVES.
DISCUSSION OF DR. CHERYL GRAHAM'S LEAVING.

28-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: MINUTES FROM LAST ACE INHIBITOR PLANNING
MEETING.
CONTACT PERSON: BONGIOVANNI, K.
FAXED INFORMATION RE: ATTACHED ARE FDA MINUTES OF
LAST PLANNING MEETING (20-MAR) IN PREPARATION FOR
A CARDIO-RENAL ADVISORY COMMITTEE MEETING TO BE
HELD 06-JUN AND 07-JUN.

28-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: UPDATE STATUS OF PHARMACOLOGY REVIEW.
CONTACT PERSON: RESNICK, CHARLES PH.D.
TELEPHONE CONVERSATION RE: UPDATE ON DR. VAN
ARSDDEL'S PROGRESS COMPLETING THE PHARMACOLOGY
REVIEW. STATUS HAS NOT CHANGED; HE WOULD NOT
SPECULATE ON A COMPLETION DATE.

28-MAR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: CONFIRM ATTENDANCE AT REVIEW OF QUIET
PROTOCOL.
CONTACT PERSON: BONGIOVANNI, K.
TELEPHONE CONVERSATION RE: CONFIRMED OUR
ATTENDANCE AT A MEETING TO DISCUSS THE QUIET
PROTOCOL ON 12-APR AT 9:30 AM IN ROOM 16B45.
SEE MEMO FOR LIST OF ATTENDING FDA MEMBERS.
STILL NO WORD ON THE STATUS OF THE PHARMACOLOGY
APPROVAL.

01-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: CLARIFY STATUS OF PHARMACOLOGY REVIEW.
CONTACT PERSON: RESNICK, CHARLES
TELEPHONE CONVERSATION RE: INFORMED HIM THAT
DR. TEMPLE INFORMED DR. MERINO ON 25-MAR THAT
DR. VANARSDDEL HAD COMPLETED HIS REVIEW;
DR. SPIVEY STATED THAT LAST WEEK HIS REVIEW WAS
STILL NOT COMPLETED.
DR. RESNICK PROMISED TO LOOK INTO IT AND GET BACK

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01-APR-91 40 RE: GENERAL CORRESPONDENCE

CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.

CI-906

RE: RESPONDING TO 08-MAR AND 22-MAR QUESTIONS.
THESE QUESTIONS CONCERNED INFORMATION PROVIDED
IN THE THIRD SAFETY UPDATE.

02-APR-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: DELIVER DESK COPIES OF REFERENCE NO. 40,
RESPONSE TO DR. CHEN'S QUESTIONS.

CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON

SUMMARY: I DELIVERED DESK COPIES OF OUR RESPONSE
TO DR. CHEN'S QUESTIONS CONCERNING COSTART CODING
AND DENOMINATOR FOR WBC/NEUTROPHIL ANALYSES. DR.
CHEN WAS OUT OF HIS OFFICE UNTIL APR-08.

MS. BONGIOVANNI ASKED ABOUT THE AVAILABILITY OF
HARD COPY OF DATA ON QUINAPRIL FOR THE ACE
ADVISORY COMMITTEE MEETING. I INDICATED THAT EARLY
NEXT WEEK WAS OUR TARGET. SHE SAID THAT APR-12 WAS
THE LAST DATE WHICH WOULD ALLOW THE AGENCY ENOUGH
TIME TO REVIEW PRIOR TO THE NEXT PLANNING MEETING
(APR-19).

04-APR-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: STATUS OF PHARMACOLOGY REVIEW.

CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE

SUMMARY: KATHLEEN BONGIOVANNI CALLED ON APR-04, ON
BEHALF OF DR. TEMPLE AND SAID THAT THE DRAFT
PHARMACOLOGY REVIEW HAS BEEN COMPLETED BY DR.
VAN ARSDALE AND IS NOW AVAILABLE FOR REVIEW BY
DRS. CHEN AND LIPICKY.

04-APR-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP ON QUINAPRIL REVIEW

CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON

SUMMARY: MS. BONGIOVANNI CONFIRMED THAT THE PHARM-
ACOLOGY REVIEW WAS NOW WITH DR. LIPICKY. SHE FELT
DR. CHEN AND DR. LIPICKY WILL WORK ON THE
SECONDARY REVIEW TOGETHER. WHILE IT WILL CLEARLY
BE DR. CHEN'S TOP PRIORITY UPON HIS RETURN FROM
VACATION ON APR-08, SHE COULD NOT GUARANTEE DR.
LIPICKY WILL WORK ON IT IMMEDIATELY. THERE IS
ACTUALLY ONLY A FEW DAYS OF WORK LEFT; IT IS HOPED
THAT THE NDA WILL BE WITH DE. TEMPLE THIS MONTH.

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04-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO APR-01 CONTACT.
CONTACT PERSON: RESNICK, CHARLES VIA IN PERSON
SUMMARY: DR. RESNICK INFORMED ME THAT DR. VAN ARSDEL COMPLETED HIS DRAFT REVIEW. IT WAS NOW WITH DR. LIPICKY; DR. RESNICK DID NOT REVIEW IT. I EXPLAINED THAT I THOUGHT DR. CHEN WOULD DO THE SECONDARY (DIVISIONAL) REVIEW. DR. RESNICK FELT DR. LIPICKY WISHED TO SEE THE REVIEW DUE TO ITS DELAY.
I THANKED DR. RESNICK FOR THE INFORMATION. HE WILL LIKELY NOT BE INVOLVED AGAIN UNTIL THE FINAL LABELING DISCUSSIONS OR FINALIZATION OF THE SBA.

09-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FINAL (?) QUESTION ON NDA REVIEW.
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE
SUMMARY: DR. CHEN WANTED TO KNOW IF WE HAD EVER RESPONDED TO HIS EARLIER REQUEST CONCERNING THE PROPER "N" FOR NEUTROPHILS AND WBC. HE WAS INFORMED THAT THE SUBMISSION WAS DELIVERED ON APRIL 2. DR. CHEN CHECKED HIS COPY AND APOLOGIZED FOR THE OVERSIGHT.
DR. CHEN ALSO WISHED TO ASK OUR DEFINITION OF "END-OF-STUDY". IF A LABORATORY VALUE RETURNED TO NORMAL AT THE END-OF-STUDY, WAS THE PATIENT STILL ON DRUG? AFTER CHECKING WITH DR. KNAPP, DR. CHEN WAS INFORMED THAT, EXCEPT IN RARE INSTANCES, PATIENTS WERE ON DRUG DURING THIS FINAL LABORATORY MEASUREMENT.
DR. CHEN HAS SEEN, BUT NOT YET REVIEWED CAREFULLY, THE DRAFT PHARMACOLOGY REVIEW. HE WILL NEED TO MEET WITH DR. LIPICKY TO INCORPORATE THE PHARMACOLOGY SECTION INTO HIS SECONDARY (DIVISIONAL) REVIEW. CONTINUED: SEE CENTRAL FILE COPY.

09-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: LIST OF ATTENDEES AT QUIET PROTOCOL REVIEW.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
SUMMARY: I CALLED MS. BONGIOVANNI TO TELL HER THAT WE WOULD HAVE SIX REPRESENTATIVES AT THE MEETING ON APRIL 12. WE WILL HAVE REPRESENTATIVES FROM CLINICAL DEVELOPMENT, BIOMETRICS, AND REGULATORY AFFAIRS. A LIST OF ATTENDEES WILL BE SUBMITTED TO FDA TOMORROW.
ON A SEPARATE MATTER, I INDICATED THAT WE WOULD LIKELY HAVE DATA FOR THE ACE-1 ADVISORY COMMITTEE MEETING TO THE AGENCY ON APRIL 12, IF NOT THEN, ON MONDAY APRIL 15.

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11-APR-91 LETTER RE: CARDIOVASCULAR RENAL DRUG ADVISORY COMMITTEE
CONTENT:

LETTER TO: BONGIOVANNI, KATHLEEN MS.
RE: ATTACHED ARE THE DATA WHICH WE AGREED TO
PROVIDE FOR THE UPCOMING CARDIOVASCULAR AND RENAL
DRUG ADVISORY COMMITTEE MEETING IN JUNE. WE
BELIEVE WE HAVE PRESENTED THE DATA IN THE FORMAT
AGREED UPON AT OUR PLANNING MEETING ON MARCH 20,
1991.
DR. LLOYD KNAPP (CLINICAL DEVELOPMENT), AND I WILL
BE IN ATTENDANCE AT THE NEXT MEETING TO BE HELD ON
APRIL 19, 1991. IF YOU HAVE QUESTIONS CONCERNING
THE PROVIDED INFORMATION, PLEASE DON'T HESITATE TO
CONTACT ME

11-APR-91 41 LETTER RE: GENERAL CORRESPONDENCE
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
RE: WE ARE RESPONDING TO QUESTIONS AND COMMENTS
FROM THE BIOPHARMACEUTICS DIVISION REGARDING OUR
PENDING NDA 19-885 FOR ACCUPRIL (QUINAPRIL
HYDROCHLORIDE) TABLETS. WE RECEIVED THESE COMMENTS
VIA DR. SHAW CHEN, OF YOUR DIVISION, ON MARCH 20,
1991.
FOR EASE OF REVIEW, WE HAVE REPEATED THE QUESTIONS
AND COMMENTS FOLLOWED BY OUR RESPONSES IN AN
ATTACHMENT TO THIS LETTER. WE BELIEVE WE HAVE
UNDERSTOOD AND ADEQUATELY ADDRESSED THESE
QUESTIONS AND COMMENTS FROM THE BIOPHARMACEUTICS
DIVISION.
IF WE CAN BE OF FURTHER ASSISTANCE, PLEASE DO NOT
HESITATE TO CONTACT THE UNDERSIGNED AT 313/996-
7756.
CONTINUED: SEE CENTRAL FILE COPY FOR ATTACHMENTS.

12-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: PROVIDE COPIES OF DATA FOR ACE INHIBITOR
ADVISORY COMMITTEE MEETING
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
SUMMARY: I DELIVERED A COPY OF DATA FOR QUINAPRIL
("BESTAPRIL") WHICH WILL BE PRESENTED BY FDA AT
THE JUNE 6-7 ADVISORY COMMITTEE MEETING. THE
FORMAT, ECT., WILL BE REVIEWED AT THE NEXT
PLANNING MEETING AT FDA ON APRIL 19, 1991 (DRS.
KNAPP & SPIVEY TO ATTEND).
I THEN ASKED MS. BONGIOVANNI IF DR. DERN (MEDICAL
REVIEWER) HAD ANY FEEDBACK ON THE CLINICAL SECTION
OF THE ACCURETIC NDA, AS WE HAD ALREADY RECEIVED
QUESTIONS ON THE CMC SECTION. SHE SAID SHE WOULD
CHECK AND LET ME KNOW.

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12-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS OF QUINAPRIL REVIEW.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
SUMMARY: MS. BONGIOVANNI INDICATED THAT DR. CHEN
AND DR. LIPICKY HAD NOT YET MET TO REVIEW THE
PHARMACOLOGY SECTION OF THE DIVISIONAL REVIEW. ONE
REASON FOR THE DELAY WAS DR. LIPICKY'S COMMAND
PERFORMANCE WITH DR. TEMPLE BEFORE A CONGRESSIONAL
PANEL (SEE ATTACHED SUMMARY). MS. BONGIOVANNI WAS
CONFIDENT, HOWEVER, THAT THE NDA WOULD BE TO
DR. TEMPLE BY THE END OF APRIL.

12-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS OF QUINAPRIL INSPECTION
CONTACT PERSON: WOLTERS, ROBERT VIA IN PERSON
SUMMARY: WHILE I WAS STANDING IN THE HALLWAY AT
THE FDA, DR. WOLTERS ASKED ME IF WE HAD EVER
RECEIVED OUR SITE INSPECTION OF MOPS FOR
QUINAPRIL. I INFORMED HIM THAT WE HAD IN JANUARY
AND PASSED WITH FLYING COLORS. DR. WOLTERS STILL
HAD NOT RECEIVED NOTIFICATION FROM COMPLIANCE.
I NOTED THAT WE ARE NOW ONLY A FEW WEEKS AWAY FROM
APPROVAL AND THAT I WAS CONCERNED HE HAD NOT YET
HEARD FROM COMPLIANCE. I PROMISED TO FOLLOW UP ON
OUR END WITH NEWARK AND/OR COMPLIANCE HEAD-
QUARTERS. DR. WOLTERS THANKED ME FOR THE EFFORT.

12-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: REQUEST FOR SAMPLE SLIDE FOR ADVISORY
COMMITTEE PLANNING MEETING (4-19-91).
CONTACT PERSON: FENICHEL, R. M.D. VIA IN PERSON
SUMMARY: DR. FENICHEL STOPPED ME IN THE HALLWAY
AT FDA TO DISCUSS FORMATS FOR SLIDE PREPARATION
FOR OUR NEXT ADVISORY COMMITTEE PLANNING MEETING
(4-19-91). WE DISCUSSED THE VARIOUS FORMATS
(INCLUDING HARVARD GRAPHICS, WHICH WE USE) AND HE
REQUESTED AN EXAMPLE SLIDE FOR THE NEXT MEETING.
HE WILL PROVIDE A SLIDE ALONG WITH THE NECESSARY
DESCRIPTION OF COLORS, ECT.

15-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: QUESTION ON BIOPHARM. RESPONSE SUBMITTED
4/12.
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE
SUMMARY: DR. CHEN AND DR. SAMARA (FROM BIOPHARM.)
HAD BOTH REVIEWED OUR APRIL 11 SUBMISSION WHICH
CONTAINED OUR RESPONSES TO DR. SAMARA'S REVIEW OF
THE NDA. DR. SAMARA NEEDED CLARIFICATION OF THE
LOCATION OF THE PK PARAMETERS REFERENCED IN
RESPONSE NUMBER 3. ALL OTHER RESPONSES WERE
REVIEWED WITHOUT FURTHER COMMENT. DR. CHEN
SUGGESTED WE TELEPHONE DR. SAMARA DIRECTLY WITH

THIS INFORMATION (443-0260).
DR. CHEN STILL HAD NOT MET WITH DR. LIPICKY
CONCERNING THE PHARMACOLOGY REVIEW, THOUGH HE HAS
REVIEWED IT HIMSELF. HE IS NOW AWARE OF WHERE THE
ISSUES MIGHT BE. HE ALSO AGREED WE ARE GETTING
QUITE CLOSE TO SENDING THE NDA TO DR. TEMPLE.

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FDA CONTACT MEMO

MEMO RE: STATUS OF QUINAPRIL INSPECTION
CONTACT PERSON: CUNNINGHAM, D. VIA TELEPHONE
SUMMARY: I CALLED MS. CUNNINGHAM TO INFORM HER
THAT MR. D. MULLIGAN (COMPLIANCE DIVISION, NEWARK
DISTRICT), THE INSPECTOR FOR QUINAPRIL, CONFIRMED
THAT THE INSPECTION REPORT WAS SENT TO METRO PARK
NORTH (COMPLIANCE DIVISION) IN FEBRUARY OF THIS
YEAR. SHE SAID THAT SHE COULD NOT CONTACT
COMPLIANCE DIRECTLY BUT HAD TO GO THROUGH LINDA
CARTER (CDER I). SHE SUGGESTED THAT I CONTACT
COMPLIANCE DIRECTLY. I TOLD HER THAT PREVIOUS
ATTEMPTS TO INQUIRE ABOUT INSPECTION REPORTS BY AN
ASSOCIATE (D. THOMAS) WERE NOT RESPONDED TO BY THE
COMPLIANCE DIVISION. MY ASSOCIATE WAS TOLD BY
COMPLIANCE TO CONTACT THE CSO FOR THE GROUP
REVIEWING THE DRUG.

15-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: REVIEW REQUEST FOR SUMMARY
PHARMACOKINETICS PARAMETERS STUDY 906-305
CONTACT PERSON: SAMARA, EMIL DR. VIA TELEPHONE
SUMMARY: I CALLED DR. SAMARA TO CLARIFY HIS
REQUEST FOR MORE INFORMATION FROM STUDY 906-305.
HE WANTS THE STANDARD ANALYSIS AND SUMMARY
PHARMACOKINETIC PARAMETERS (TMAX, CMAX, ECT.) TO
BE PROVIDED. WE WILL PROVIDE THIS FOR HIS REVIEW.
DR. SAMARA ALSO MENTIONED THE MARKET-IMAGE FOOD
EFFECT STUDY AND SAID HE WAS SATISFIED WITH THE
TIME-FRAME FOR SUBMITTING (END OF MONTH).
FINALLY, DR. SAMARA (REFERRING TO RESPONSE #2 ON
PROTEIN BINDING) TOOK US UP ON OUR OFFER TO
PROVIDE SUMMARY DATA. HE INDICATED THIS WAS NOT AN
APPROVAL ISSUE.

17-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: REQUEST FOR DATA POINTS ON A SLIDE
PROVIDED TO FDA FOR ACE INHIBITOR
ADVISORY COMMITTEE MEETING.
CONTACT PERSON: FENICHEL, R. M.D. VIA TELEPHONE
SUMMARY: DR. FENICHEL ASKED FOR US TO PROVIDE DATA
POINTS FOR OUR SLIDE LEK22, PROVIDED TO FDA ON
APRIL 12, 1991 FOR USE IN THE ADVISORY COMMITTEE
MEETING IN JUNE. HE WANTS TO CREATE HIS OWN SLIDE
FOR ILLUSTRATIVE PURPOSES AT THE NEXT PLANNING
MEETING ON APRIL 19, 1991. I SAID I WOULD FAX THE
INFORMATION TO HIM TODAY OR EARLY TOMORROW.

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FDA CONTACT MEMO

MEMO RE: STATUS OF QUINAPRIL REVIEW.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
SUMMARY: WHILE SPEAKING TO MS. BONGIOVANNE ABOUT
ANOTHER TOPIC, I ASKED ABOUT THE STATUS OF THE
QUINAPRIL REVIEW. SHE SAID THAT AS OF TWO DAYS
AGO DR. CHEN WAS STILL REVIEWING THE PHARMACOLOGY
REVIEW OF DR. VAN ARSDEL. SHE DID NOT KNOW IF DR.
CHEN AND DR. LIPICKY HAD MET TO DISCUSS YET.

19-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: CHECK STATUS OF ACCUPRIL REVIEW
CONTACT PERSON: CHEN, SHAW DR. VIA IN PERSON
SUMMARY: I MET WITH DR. CHEN TO DISCUSS THE
APPROVAL STATUS OF QUINAPRIL. HE SAID THAT HE HAD
COMPLETED HIS REVIEW OF THE PHARMACOLOGY REVIEW
(DR. VANARSDEL) AND SENT HIS (DR. CHEN'S REVIEW)
TO DR. LIPICKY. DRS. CHEN AND LIPICKY WILL MEET IF
ANY ISSUES ARE APPARENT. I THEN ASKED DR. CHEN FOR
HIS FEEBACK ON OUR PROPOSED LABELING. HE HAS
REVIEWED THE LABELING AND HIS COMMENTS WERE BY-AND-
-LARGE EDITORIAL, OR ONES THAT COULD BE CONSIDERED
IN THE REALM OF CLASS LABELING. HE DID WANT US TO
PROVIDE THE FOLLOWING:
1) A COPY OF THE LABELING IN LANDSCAPE FORMAT, I.E
TEXT ON LEFT SIDE BLANK SPACE ON RIGHT SIDE.
2) IN THE PHARMACODYNAMICS SECTION INCLUDE A
STATEMENT ABOUT PATIENT WITHDRAWALS, I.E., WHAT
HAPPENED TO BLOOD PRESSURE?
CONTINUED - SEE CENTRAL FILE COPY.

23-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: DISCUSS LABELING SUBMISSION FORMAT
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
SUMMARY: I INFORMED MS. BONGIOVANNI THAT WE WERE
IN THE PROCESS OF RESPONDING TO DE. CHEN'S
LABELING REQUESTS MADE TO RICH SPIVEY ON 4/19.
MS. BONGIOVANNI INFORMED ME THAT THEY HAVE NO
SPECIFIC FORMAT REQUESTS FOR DRAFT LABELING, OTHER
THAN SUFFICIENT SPACE IN A RIGHT-HAND COLUMN TO
MAKE COMMENTS AND ADDITIONS. LANDSCAPE VS.
PORTRAIT WAS NOT A CONCERN. THEY ALSO HAVE NO USE
FOR WORD PROCESSING DISKS AS DR. TEMPLE WILL MAKE
HIS COMMENTS DIRECTLY ON THE HARD COPY.
MS. BONGIOVANNI ASKED WHEN THE LABELING WOULD BE
SUBMITTED; I REPLIED I WOULD HAND DELIVER IT ON
THURSDAY. SHE SUGGESTED SUBMITTING BY FAX TO DR.
CHEN IF WE HAVE IT AVAILABLE EARLY ON WEDNESDAY.
MS. BONGIOVANNI ALSO NOTED THAT DR. LIPICKY HAS
DR. CHEN'S REVIEW. HE IS IN ATLANTA UNTIL FRIDAY,
BUT SHE STILL FEELS THE NDA SHOULD BE TO DR.
TEMPLE BY THE END OF THE MONTH.

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23-APR-91 MINUTES OF FDA MEETING
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DATE: 19-APR-91
PLANNING MEETING FOR JUNE ADVISORY COMMITTEE
MEETING CARDIOVASCULAR AND RENAL DRUG PRODUCTS.

24-APR-91 42 LETTER RE: REVISED DRAFT LABELING
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
RE: REFERENCE IS MADE TO AN APRIL 19, 1991
CONVERSATION WITH DR. SHAW CHEN, OF YOUR DIVISION,
CONCERNING LABELING FOR OUR PENDING NDA 19-885,
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.
ENCLOSED IS THE REVISED DRAFT LABELING PRESENTED
IN THE REQUESTED TWO-COLUMN FORMAT. THE FOLLOWING
CHANGES WERE INSTITUTED:
PAGE 4
CLINICAL PHARMACOLOGY:
ADDED A SENTENCE REGARDING ANTI-HYPERTENSIVE
EFFECT IN BLACK PATIENTS.
INDICATIONS AND USAGE:
ADDED A PARAGRAPH REGARDING AGRANULOCYTOSIS.
PAGE 5
WARNINGS:
ADDED A SENTENCE REGARDING ANGIOEDEMA NOT
ASSOCIATED WITH ACE INHIBITORS.
CONTINUED - SEE CENTRAL FILE COPY.

25-APR-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: DELIVER LABELING AND CHECK ON STATUS OF
REVIEW.
CONTACT PERSON: CHEN, SHAW DR. VIA IN PERSON
SUMMARY: I PROVIDED DR. CHEN A DESK COPY OF THE
LABELING CHANGES WHICH HE HAD REQUESTED LAST WEEK.
HE NOTED THAT THE FORMAT WAS EXACTLY WHAT HE WAS
LOOKING FOR.
I ALSO ASKED DR. CHEN IF THERE WERE ANY CONCERNS
HE HAD THAT HE HAD TO REVIEW WITH DR. LIPICKY
PRIOR TO THE NDA GOING TO DR. TEMPLE. DR CHEN
EXPRESSED FRUSTRATION THAT THE PHARMACOLOGY REVIEW
WAS SO LATE; HE HAD ISSUES THAT HE NEEDS TO
DISCUSS WITH DR. LIPICKY THAT SHOULD NOT HAVE HAD
TO WAIT FOR THE LAST MINUTE. THESE POTENTIAL
ISSUES WERE RAISED IN THE STATISTICAL REVIEW OF
THE CARCINOGENICITY STUDIES.
THE BIOMETRICS REVIEWER QUESTIONED WHETHER THE
DOSES USED THE MOUSE STUDY WERE HIGH ENOUGH IN
THAT LITTLE TOXICITY WAS SEEN OTHER THAN WEIGHT
LOSS. CONTINUED - SEE CENTRAL FILE COPY.

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25-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF REVIEWS AND DELIVER DESK COPIES
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
SUMMARY: I PROVIDED MS. BONGIOVANNI WITH DESK
COPIES OF THE NEW LABELING FOR QUINAPRIL AND THE
SAFETY UPDATE FOR ACCURETIC.
MS. BONGIOVANNI NOTED THAT THIS WOULD BE A GOOD
TIME TO SUBMIT THE FINAL PRINTED LABELS FOR
CARTONS AND CONTAINERS. SHE ALSO ASKED ABOUT THE
STATUS OF OUR ADVERTISING. I NOTED THAT WE HOPED
TO PROVIDE IT TO THE DRUG ADVERTISING DIVISION
SHORTLY, BUT THOUGHT THAT THAT WAS NOT CRITICAL
FOR APPROVAL. MS. BONGIOVANNI AGREED THAT,
TECHNICALLY, THE ADVERTISING IS "REQUESTED" AND
NOT REQUIRED FOR APPROVAL, BUT ALSO NOTED THAT DR.
TEMPLE HAS BEEN KNOWN TO HOLD APPROVALS UNTIL
SOMEONE IN THE REVIEW DIVISION HAS REVIEWED THE
LAUNCH PROMOTINAL MATERIALS.
I NOTED WE WOULD BE SURE TO SUBMIT THESE MATERIALS
WITHIN A COUPLE OF WEEKS.
CONTINUED - SEE CENTRAL FILE COPY.

25-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: RAT BIOASSAY STUDY
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE
ABSTRACT: DR. CHEN REQUESTED CONFIRMATION THAT
SLIDES FROM THE RAT BIOASSAY STUDY WERE READ IN A
BLINDED FASHION. WE SHOULD INDICATE WHERE IN THE
NDA SUCH STATEMENT EXISTS OR PROVIDE SUCH A
STATEMENT IN WRITING IF THAT IS CORRECT.

25-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: FDA BIOMETRICS REVIEW
CONTACT PERSON: LIPICKY, RAY DR. VIA IN PERSON
ABSTRACT: CONCERNED OVER FDA BIOMETRICS REVIEW
OF CARCINOGENICITY STUDIES.

26-APR-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: REQUEST LOCATION OF DESCRIPTION OF
BLINDING REGIMEN IN CARCINOGENICITY
STUDIES.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
ABSTRACT: REQUEST LOCATION OF DESCRIPTION OF
BLINDING REGIMEN IN CARCINOGENICITY STUDIES.

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26-APR-91 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO 4/25 VIST AND CONVERSATION WITH DR. LIPICKY. CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE ABSTRACT: FOLLOW-UP TO 4/25 VISIT AND CONVERSATION WITH DR. LIPICKY.
29-APR-91 CONTENT:		FDA CONTACT MEMO MEMO RE: CONFIRM RESOLUTION OF ISSUE RAISED BY DR. LIPICKY ON 4/25. CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE ABSTRACT: CONFIRM RESOLUTION OF ISSUE RAISED BY DR. LIPICKY ON 4/25.
29-APR-91 CONTENT:		FDA CONTACT MEMO MEMO RE: REQUEST ADDITIONS TO QUINAPRIL LABELING CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE ABSTRACT: REQUEST ADDITIONS TO QUINAPRIL LABELING.
30-APR-91 CONTENT:		FDA CONTACT MEMO MEMO RE: QUESTIONS ON SBA PAGES 76 AND 78. CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE MEMO FROM: SPIVEY, R. SUMMARY: DR. CHEN CALLED TO CLAIRFY THE GRAPHS GIVEN ON P. 76 AND 78 OF THE SBA. OUR MOST RECENT UPDATES OF THESE TWO PAGES HAVE SWITCHED THE GRAPHS, I.E. FIGURE 15 ON PAGE 76 SHOULD BE ON PAGE 78 AND VICE VERSA. NOTE THAT THE FIGURE TITLES ARE CORRECT, THE FIGURES HAVE BEEN TRANSPOSED. I AGREED TO SEND HIM CORRECTED PAGES.
01-MAY-91 CONTENT:		FDA CONTACT MEMO MEMO RE: STATUS OF LAST MINUTE ITEMS BEFORE NDA GOES TO DR. TEMPLE. CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, IRWIN ABSTRACT: DESCRIPTION OF CARCINOGENICITY STUDY BLINDING PROCEDURE ONLY OUTSTANDING ITEM.
01-MAY-91 CONTENT:		FDA CONTACT MEMO MEMO RE: ACCUPRIL NDA SUPPLEMENTS CONTACT PERSON: CUNNINGHAM, D. VIA IN PERSON MEMO FROM: BRENNAN, S ABSTRACT: CONTENT OF ACCUPRIL NDA SUPPLEMENTS FOR 40-MG TABLET AND TECH TRANSFER DISCUSSED.

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01-MAY-91 43 LETTER RE: REVISED LABELING

CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: MARTIN, IRWIN
RE: WE ARE RESPONDING TO AN APRIL 29, 1991 REQUEST
FROM DR. SHAW CHEN, OF YOUR DIVISION, CONCERNING
OUR PENDING NDA 19-885 FOR QCCUPRIL (QUINAPRIL
HYDROCHLORIDE) TABLETS. DR. CHEN REQUESTED THAT WE
PROVIDE ADDITIONAL WORDING IN THE PRECAUTIONS
SECTION ADDRESSING USE OF ACCUPRIL IN GERIATRIC
PATIENTS. ATTACHED IS A REVISED LABELING PAGE WITH
THE REQUESTED NEW INFORMATION. THIS PAGE REPLACES
PAGE 12 OF OUR SUBMISSION OF APRIL 24, 1991
(REF. NO. 42).
SEE ATTACHEMENTS

02-MAY-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: COMPLIANCE INSPECTION REPORT FOR
ACCUPRIL.
CONTACT PERSON: CUNNINGHAM, D. MS VIA TELEPHONE
MEMO FROM: BRENNAN, S.
ABSTRACT: COMPLIANCE INSPECTION REPORT FOR
ACCUPRIL RECEIVED BY DIVISION OF CARDIO-RENAL.

02-MAY-91 44 LETTER RE: SBA; RAT CARCINOGENICITY REPORT

CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: MARTIN, IRWIN
RE: WE ARE RESPONDING TO AN APRIL 30, 1991 REQUEST
FROM DR. SHAW CHEN, OF YOUR DIVISION, CONCERNING
THE DRAFT SUMMARY BASIS OF APPROVAL (SBA) OF OUR
PENDING NDA FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE)
TABLETS. DR. CHEN ASKED THAT WE PROVIDE CORRECTED
FIGURES FOR FIGURE 15 (PAGE 76) AND FIGURE 17
(PAGE 78) OF THE DRAFT SBA. WE HAVE PROVIDED, IN
ATTACHEMENT 1, REPLACEMENT PAGES 76 AND 78 FOR THE
SBA, SUBMITTED OCTOBER 31, 1991, (REF. NO. 18) AND
REVISED NOVEMBER 27, 1990 (REF. NO. 24).
WE ARE ALSO PROVIDING IN ATTACHMENT 2, PER A MAY
1, 1991 REQUEST COMMUNICATED BY MS. KATHLEEN
BONGIOVANNI OF YOUR DIVISION, A SUMMARY OF THE
PROCEDURE USED BY A PEER REVIEW PANEL OF EXPERT
PATHOLOGISTS TO EVALUATE HISTOLOGY SLIDES FROM THE
RAT CARCINOGENICITY STUDY (RR 745-01173, VOL 20,
P. 002431, JAN 26, 1989).
CONTINUED - SEE CENTRAL FILE COPY.

03-MAY-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP TO 5/1 REQUEST ON
CARCINOGENICITY STUDY SLIDE BLINDING.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, IRWIN
ABSTRACT: FOLLOW-UP TO 5/1 REQUEST ON
CARCINOGENICITY STUDY SLIDE BLINDING.

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06-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: DETERMINE STATUS OF FOSENAPRIL NDA; DETERMINE STATUS OF LIPICKY QUINAPRIL REVIEW. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, IRWIN ABSTRACT: DETERMINE STATUS OF FOSENAPRIL NDA; DETERMINE STATUS OF LIPICKY QUINAPRIL REVIEW.
07-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO APRIL 15 CONTACT RE: BIOPHARM REVIEW OF 906-305. CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: FOLLOW-UP TO APRIL 15 CONTACT RE: BIOPHARM REVIEW OF 906-305.
08-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF QUINAPRIL NDA REVIEW CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: THE QUINAPRIL NDA IS LIKELY TO BE TO DR. TEMPLE ON FRIDAY, MAY 10. JUNE 6/7 ADVISORY COMMITTEE TOPIC CHANGED; WILL NO LONGER BE ABOUT ACES (SEE ATTACHED).
10-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: NDA TO DR. TEMPLE 5/10 OR 5/13.
13-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: NDA SENT TO DR. TEMPLE.
14-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: DRAFT AGENDA FOR JUNE 6-7 ADVISORY COMMITTEE. CONTACT PERSON: BONGIOVANNI, K VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: DRAFT AGENDA FOR JUNE 6-7 ADVISORY COMMITTEE.

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20-MAY-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: HOW TO SUBMIT "FOOD-EFFECT" STUDY.
CONTACT PERSON: BONGIOVANNI, D. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: DISCUSSION OF SUBMISSION OF "FOOD-EFFECT" STUDY.

23-MAY-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: REQUEST SLIDES FOR OCTOBER CARDIO-RENAL
ADVISORY COMMITTEE MEETING.
CONTACT PERSON: BONGIOVANNI, K.
MEMO FROM: SPIVEY, R.
ABSTRACT: REQUEST SLIDES FOR OCTOBER CARDIO-RENAL
ADVISORY COMMITTEE MEETING.

24-MAY-91
CONTENT:

45 LETTER RE: GENERAL CORRESPONDENCE

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: MARTIN, IRWIN
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS. AS
NOTED IN OUR SUBMISSION OF APRIL 11, 1991 (REF. NO
41), WE ARE PROVIDING THE REPORT OF STUDY 906-369,
A STUDY OF THE EFFECT OF A HIGH FAT MEAL ON THE
BIOAVAILABILITY OF QUINAPRIL MARKET-IMAGE TABLETS.
THE FINDINGS FROM THIS STUDY ARE NOT IN AGREEMENT
WITH THOSE SUBMITTED IN OUR ORIGINAL NDA. WE ARE,
THEREFORE, PROPOSING THAT THE FOLLOWING
CHANGES BE MADE TO THE DRAFT LABELING FOR
ACCUPRIL.
CONTINUED - SEE CENTRAL FILE COPY.

28-MAY-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: DISCUSS SUBMISSION STRATEGY FOR FOOD
EFFECT STUDY.
CONTACT PERSON: ROEDER, DAVID VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: DISCUSS SUBMISSION STRATEGY FOR FOOD
EFFECT STUDY.

29-MAY-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: FOLLOW-UP TO 5/28 CONVERSATION.
CONTACT PERSON: ROEDER, DAVID VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: DR. TEMPLE DID NOT THINK THE FOOD EFFECT
STUDY WOULD SLOW DOWN THE NDA APPROVAL.

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30-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: QUESTION ON FOOD EFFECT STUDY. CONTACT PERSON: SAMARA, EMIL VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: QUESTION ON FOOD EFFECT STUDY.
31-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: DETERMINE WHETHER WE CAN SUBMIT LAUNCH MATERIALS PRIOR TO RECEIPT OF APPROVABLE LETTER. CONTACT PERSON: KNIPPEN, M. VIA TELEPHONE MEMO FROM: SPIVEY, R. ABSTRACT: DETERMINE WHETHER WE CAN SUBMIT LAUNCH MATERIALS PRIOR TO RECEIPT OF APPROVABLE LETTER.
31-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: NDA UPDATE. CONTACT PERSON: ROEDER, DAVID MEMO FROM: MARTIN, I. ABSTRACT: NDA UPDATE.
31-MAY-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO 5/30 TELEPHONE CALL. CONTACT PERSON: SAMARA, EMIL MEMO FROM: MARTIN, I. ABSTRACT: - CONFIRMATORY CALCULATIONS PROVIDED TO DR. SAMARA - DR. SAMARA HAS COMPLETED REVIEW OF FOOD EFFECT STUDY. - MINOR QUESTIONS ON METHODOLOGY RECEIVED; NOT APPROVAL-RELATED.
05-JUN-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF TEMPLE'S NDA REVIEW. CONTACT PERSON: ROEDER, DAVID VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: DR. TEMPLE HAD NOT YET BEGUN HIS REVIEW.
07-JUN-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: DRUG PRODUCT MANUFACTURING SITES FOR NDAS CONTACT PERSON: ZOSCHNICK, M. VIA TELEPHONE MEMO FROM: BRENNAN, S. SUMMARY: MR. ZOSCHNICK CALLED REGARDING THE DRUG PRODUCT MANUFACTURING SITES FOR SIX OF OUR PENDING NDAS. HE EXPLAINED THAT THE DETROIT OFFICE RECEIVED A LIST OF SIX NDAS FROM THE WASHINGTON

COMPLIANCE OFFICE WHICH COULD BE APPROVED IN THE
NEXT 12 MONTHS. THESE APPLICATIONS WERE:
SEE MEMO.

I ASKED HIM IF HE WAS INTERESTED IN THE DRUG
SUBSTANCE MANUFACTURING SITES BECAUSE MOST OF THE
DRUG PRODUCTS HE INQUIRED ABOUT WERE MANUFACTURED
OUTSIDE THE DETROIT DISTRICT. HE SAID HIS PRIMARY
INTEREST WAS DRUG PRODUCT MANUFACTURING SITES.
IN RESPONSE TO HIS REQUEST, THE ATTACHED SUMMARY
TABLES WERE SENT TO HIM BY TELECOPY. THE TABLES
SUMMARIZE THE MANUFACTURING AND PACKAGING SITES
LISTED IN OUR PENDING NDAS.

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24-JUN-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: NDA STATUS
CONTACT PERSON: BONGIOVANNI, D. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: NDA STATUS.

27-JUN-91 LETTER RE: ANNUAL REPORT

CONTENT:

LETTER TO: SCHALL, THOMAS
LETTER FROM: SPIVEY, RICHARD
RE: IN ACCORDANCE WITH THE DRUG EXPORT AMENDMENTS
ACT OF 1986, WE ARE PROVIDING A SUMMARY OF ACTIONS
TAKEN BY PARKE-DAVIS/WARNER-LAMBERT IN PURSUIT OF
MARKETING APPROVAL OF QUINAPRIL DURING THE PAST
YEAR. PLEASE REFER TO OUR DRUG EXPORT APPLICATIONS
END-0058, END-0058A01 AND END-0058A02.
THE NEW DRUG APPLICATION FOR QUINAPRIL (NDA 19-
885) WAS SUBMITTED TO THE FOOD AND DRUG ADMINIS-
TRATION ON 26-JAN-89. THE APPLICATION IS CURRENTLY
UNDER ACTIVE REVIEW BY THE DIVISION OF CARDIO-
RENAL DRUG PRODUCTS, OFFICE OF DRUG EVALUATION I.
IN THIS REPORTING PERIOD PARKE-DAVIS HAS SUBMITTED
DRAFTS OF THE SUMMARY BASIS OF APPROVAL, TWO ADD-
ITIONAL SAFETY UPDATES AND REVISIONS OF THE PRO-
POSED LABELING WITH SUPPORTING DOCUMENTATION.
WE BELIEVE THAT THE ABOVE INFORMATION SEVERS TO
DOCUMENT OUR ACTIVE PURSUIT OF APPROVAL OF THE
QUINAPRIL NEW DRUG APPLICATION.

02-JUL-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP TO TELEPHONE MESSAGES OF 6/27
AND 6/28.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: FOLLOW-UP TO TELEPHONE MESSAGES OF 6/27
AND 6/28.

10-JUL-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP TO REQUEST OF 7/2; STATUS OF
NDA REVIEWS.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: FOLLOW-UP TO REQUEST OF 7/2; STATUS OF
NDA REVIEWS.

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16-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO 7/15 MEETING; INFORM OF MERINO DISCUSSION WITH TEMPLE. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE ABSTRACT: NDA TO GP TO CAC PER DR. TEMPLE, BUT NOT NECESSARILY PRIOR TO APPROVAL.
16-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO REQUEST FOR INFORMATION ON 5-31-91. CONTACT PERSON: SAMARA, E. DR. VIA TELEPHONE MEMO FROM: SPIVEY, R. ABSTRACT: FOLLOW-UP TO REQUEST FOR INFORMATION ON 5-31-91.
18-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: ADDITIONAL QUESTIONS ON 2-YEAR RAT CARCINOGENICITY STUDY. CONTACT PERSON: VANARSDEL, W. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: ADDITIONAL QUESTIONS ON 2-YEAR RAT CARCINOGENICITY STUDY.
30-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO QUESTIONS REGARDING 2-YEAR RAT CARCINOGENICITY STUDY (SEE JULY 18). CONTACT PERSON: VAN ARSDEL, W. VIA TELEPHONE MEMO FROM: SPIVEY, R. ABSTRACT: FOLLOW-UP TO QUESTIONS REGARDING 2-YEAR RAT CARCINOGENICITY STUDY (SEE JULY 18).
31-JUL-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF NDA REVIEW. CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: STATUS OF NDA REVIEW.
02-AUG-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO 7/13 VISIT. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: CAC SCHEDULED FOR 8/16; DEFELICE TO CALL TO DISCUSS VANARSDEL REQUEST.

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06-AUG-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: CONFIRM FDA'S RECEIPT OF GLP INSPECTION
REPORT.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: SPIVEY, R.
ABSTRACT: CONFIRM FDA'S RECEIPT OF GLP INSPECTION
REPORT.

06-AUG-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: UPDATE ON NDA STATUS.
CONTACT PERSON: BONGIOVANNI, K.
MEMO FROM: MARTIN, I.
ABSTRACT: MS. BONGIOVANNI INFORMED THAT DR.
TEMPLE'S REVIEW IS NEARING COMPLETION.

12-AUG-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: TO DISCUSS THE STATUS OF THE QUINAPRIL
NDA.
CONTACT PERSON: TEMPLE, ROBERT DR. VIA TELEPHONE
MEMO FROM: MERINO, WILLIAM
ABSTRACT: TWO REMAINING ISSUES WERE DISCUSSED, ONE
WAS RESOLVED AND THE OTHER CAN BE RESOLVED AFTER
RECEIPT OF THE APPROVABLE LETTER.

14-AUG-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: UPDATE ON NDA ISSUES.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: QUINAPRIL TO BE DISCUSSED 8/15 AT
C.A.C.; APPROVABLE LETTER TO FOLLOW SHORTLY
THEREAFTER.

14-AUG-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: DISCUSS 40 MG TABLET SNDA.
CONTACT PERSON: WOLTERS, R. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: DR. WOLTERS OFFERED SUGGESTIONS FOR 40
MG TABLET SNDA.

15-AUG-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: RECEIPT OF APPROVABLE LETTER.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: APPROVABLE LETTER RECEIVED.

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15-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FEEDBACK ON CAC MEETING.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: CAC DECIDED RAT BIOASSAY WAS ACCEPTABLE;
MOUSE BIOASSAY ACCEPTABLE ONLY IF SEVERITY OF
NEPHRITIS INCREASED WITH DOSE. POST-APPROVAL
ANALYSES BY SEX WILL BE REQUESTED FOR THE SBA.

15-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: QUESTIONS DURING CAC MEETING.
CONTACT PERSON: CHEN, S. DR. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: QUESTIONS ON SEX DIFFERENCES OF
QUINAPRIL ACTION.

15-AUG-91 LETTER RE: FINAL PRINTED LABELING FOR DRUG

CONTENT:

LETTER TO: MARTIN, I.
LETTER FROM: TEMPLE, ROBERT M.D.
RE: PLEASE REFER TO YOUR 26-JAN-89 NDA SUBMITTED
UNDER SECTION 505(B) OF THE FEDERAL FOOD, DRUG,
AND COSMETIC ACT FOR ACCUPRIL (QUINAPRIL HCL) TAB.
WE ALSO ACKNOWLEDGE RECEIPT OF YOUR AMENDMENTS AND
CORRESPONDENCE DATED FROM 23-MAY-89 THROUGH
02-MAY-91. (SEE FILE COPY FOR COMPLETE DATES)
WE HAVE COMPLETED THE REVIEW OF THIS APPLICATION
AS SUBMITTED WITH DRAFT LABELING. BEFORE THE
APPLICATION MAY BE APPROVED, HOWEVER, IT WILL BE
NECESSARY FOR YOU TO SUBMIT FINAL PRINTED LABELING
FOR THE DRUG. THE LABELING SHOULD BE IDENTICAL IN
CONTENT TO THE ENCLOSED MARKED-UP DRAFT. IF
ADDITIONAL INFORMATION RELATING TO THE SAFETY OR
EFFECTIVENESS OF THIS DRUG BECOMES AVAILABLE
BEFORE WE RECEIVE THE FINAL PRINTED LABELING,
REVISION OF THAT LABELING MAY BE REQUIRED.
CONTINUED - SEE CENTRAL FILE COPY.

16-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: CHANGE IN LABELING MEETING.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: LABELING NEGOTIATIONS MEETING CHANGED TO
22-AUG-91.

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16-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: FOLLOW-UP TO CAC (2).
CONTACT PERSON: BONGIOVANNI, K.
MEMO FROM: MARTIN, I.
ABSTRACT: RODENT HEMATOLOGY AND CLINICAL CHEMISTRY
DATA REQUESTED.

20-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: QUESTIONS ON APPROVABLE LETTER LABELING
AND PROPOSED CHANGES.
CONTACT PERSON: DEFELICE, A. PH.D. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: MINOR CHANGES AGREED TO IN LABELING.
SUMMARY OF MOUSE DATA REQUESTED TO COMPLETE
QUINAPRIL FILE.

20-AUG-91 46 LETTER RE: LABELING

CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: MARTIN, I.
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR
ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA
19-885, SUBMITTED 26-JAN-89. ADDITIONAL REFERENCE
IS MADE TO THE 15-AUG-91 APPROVABLE LETTER FOR
ACCUPRIL FROM DR. TEMPLE. FURTHER REFERENCE IS
MADE TO THE UPCOMING MEETING BETWEEN PARKE-DAVIS
AND DR. TEMPLE, DR. DEFELICE AND DR. CHEN
SCHEDULED FOR THURSDAY, 22-AUG AT 4 PM. THE
PURPOSE OF THIS MEETING IS TO FINALIZE THE
LABELING FOR ACCUPRIL TABLETS.
ATTACHED ARE OUR PROPOSED REVISIONS TO THE
LABELING. THE CHANGES AS PROPOSED BY THE AGENCY
HAVE BEEN INCORPORATED INTO THE TYPED MANUSCRIPT
IN THE LEFT COLUMN OF THE ATTACHMENT; THE NEW
PARKE-DAVIS PROPOSALS ARE CONTAINED IN THE RIGHT
COLUMN.
CONTINUED - SEE FILE COPY.

21-AUG-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: CONFIRM RECEIPT OF LABELING.
CONTACT PERSON: BENTON, SANDY VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: PROPOSED FINAL LABELING RECEIVED.

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21-AUG-91 CONTENT:	47	LETTER RE: OCCURRENCE OF NEPHROPATHY LETTER TO: DEFELICE, ALBERT PH.D. LETTER FROM: MARTIN, IRWIN PH.D. RE: REFERENCE IS MADE TO OUR 15-AUG-91 TELEPHONE CONVERSATION REGARDING THE OCCURRENCE OF NEPHROPATHY IN THE MOUSE BIOASSAY FOR QUINAPRIL (NDA 19-885). YOU INDICATED THAT THE CARCINOGENICITY ASSESSMENT COMMITTEE INQUIRED WHETHER THERE WAS AN INCREASE IN SEVERITY OF NEPHROPATHY CORRESPONDING TO AN INCREASE IN DOSE. KIDNEYS FROM ALL MICE IN THE QUINAPRIL TUMOR BIOASSAY WERE EVALUATED HISTOPATHOLOGICALLY BY A CONSULTANT. THE CONSULTANT'S REPORT IS ATTACHED (RR 745-01450 PP. 37-59). A GRADING SYSTEM WAS USED TO RANK THE SEVERITY OF CHRONIC NEPHROPATHY, WHICH RANGED FROM GRADE 1 (MINIMAL) TO GRADE 5 (END-STAGE). RESULTS SHOW THAT SEVERITY OF SPONTANEOUS NEPHROPATHY WAS INCREASED IN FEMALES AT 35 AND 75 MG/KG AND IN MALES AT 75 MG/KG. THIS RESEARCH REPORT WAS SUBMITTED TO OUR NDA 19-885 ON 26-MAY-89. QUESTIONS CALL-----
22-AUG-91 CONTENT:	50	LETTER RE: TABLES OF SAFETY INFORMATION LETTER TO: LIPICKY, RAYMOND M.D. LETTER FROM: MARTIN, I. RE: REFERENCE IS MADE TO OUR PENDING NDA FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA 19-885. ADDITIONAL REFERENCE IS MADE TO OUR SUBMISSION OF PROPOSED FINAL LABELING ON 20-AUG-91. ENCLOSED PLEASE FIND THE SUMMARY TABLES OF SAFETY INFORMATION FROM THE QUINAPRIL SAFETY DATABASE UPON WHICH THE REVISED ADVERSE REACTIONS SECTION OF THE LABELING WAS BASED.
23-AUG-91 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO 8/22 MEETING. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: FINAL SUBMISSION TO PENDING NDA REVIEWED.
23-AUG-91 CONTENT:		MINUTES OF FDA MEETING DATE: 22-AUG-91 FDA MEETING RE: ACCUPRIL LABELING .

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26-AUG-91
CONTENT:

LETTER RE: JOURNAL ADVERTISEMENT, AND SALES VISUAL AID

LETTER TO: WITT, ANN (SEE REF #49 FOR ATTACHMENTS)
LETTER FROM: MARTIN, I.
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HCL) TABLETS. WE HAVE
ENCLOSED, FOR YOUR REVIEW, OUR PROPOSED 8-PAGE
JOURNAL ADVERTISEMENT AND SALES VISUAL AID, USED
IN THE INITIAL PROMOTIONAL CAMPAIGN FOR ACCUPRIL.
UNDER SEPARATE COVER THESE MATERIALS HAVE ALSO
BEEN FORWARDED TO THE DIVISION OF CARDIO-RENAL
DRUG PRODUCTS.
ALSO ENCLOSED IS OUR FINAL PRINTED LABELING WHICH
INCLUDES AGREED-UPON CHANGES FROM OUR MEETING WITH
DR. TEMPLE ON 22-AUG. THIS LABELING WAS SUBMITTED
AUG-26-91.
QUESTIONS-----

26-AUG-91
CONTENT:

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LETTER RE: FINAL PRINTED LABELING

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: MARTIN, IRWIN
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR
ACCUPRIL (QUINAPRIL HCL) TABLETS, NDA 19-885,
SUBMITTED 26-JAN-89. ADDITIONAL REFERENCE IS MADE
TO THE 15-AUG-91 APPROVABLE LETTER FOR ACCUPRIL
FROM DR. TEMPLE. FURTHER REFERENCE IS MADE TO THE
MEETING BETWEEN PARKE-DAVIS AND AGENCY
REPRESENTATIVES ON 22-AUG-91.
AS AGREED AT THE ABOVE-REFERENCED MEETING, WE ARE
SUBMITTING FINAL PRINTED LABELING WHICH IS
IDENTICAL TO THE DRAFT LABELING SUBMITTED ON
20-AUG-91 (NDA REF 46) WITH THE CHANGES AGREED TO
AT THE 22-AUG-91 MEETING. A DESCRIPTION OF THESE
CHANGES IMMEDIATELY FOLLOWS THIS COVER LETTER.
APPENDICES 1-3 INCLUDE FINAL PRINTED CARTON AND
CONTAINER LABELS WHICH ARE IDENTICAL TO THOSE
INCLUDED IN DRAFT FORM IN THE ORIGINAL NDA.
WE WILL NOT MARKET ACCUPRIL UNTIL WE HAVE RECEIVED
WRITTEN APPROVAL.

26-AUG-91
CONTENT:

49

LETTER RE: INITIAL ADVERTISING CAMPAIGN

LETTER TO: LIPICKY, RAYMOND
LETTER FROM: MARTIN, I.
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HCL) TABLETS. WE HAVE
ENCLOSED, FOR YOUR REVIEW, OUR PROPOSED 8-PAGE
JOURNAL ADVERTISEMENT AND SALES FORCE VISUAL AID
TO BE USED IN THE INITIAL ADVERTISING CAMPAIGN
FOR ACCUPRIL. UNDER SEPARATE COVER THESE MATERIALS
HAVE ALSO BEEN FORWARDED TO THE DIVISION OF
MARKETING, ADVERTISING AND COMMUNICATIONS.
ALSO ENCLOSED IS OUR FINAL PRINTED LABELING WHICH
INCLUDES AGREED-UPON CHANGES FROM OUR MEETING WITH
DR. TEMPLE ON 22-AUG. THIS LABELING WAS SUBMITTED
26-AUG-91.
QUESTIONS-----

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27-AUG-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO LABELING SUBMISSION OF 8/26.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: MS. BONGIOVANNI HAD ONE ADDITION TO
FPL; IT WILL NOT SLOW DOWN APPROVAL.

27-AUG-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO SUBMISSION OF PROMOTINAL
MATERIAL ON 26-AUG.
CONTACT PERSON: FEATHER, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: REVIEW OF PROMOTIONAL MATERIALS NOT
LIKELY UNTIL WEEK OF 09-SEP.

28-AUG-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: COMMENT ON FPL SUBMISSION.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, I. AND SPIVEY, R.
ABSTRACT: FPL FOR BLISTER PACKAGES TO BE
SUBMITTED AFTER APPROVAL.

28-AUG-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: DISCUSS ERROR IN FINAL PRINTED LABELING.
CONTACT PERSON: TEMPLE, ROBERT VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: DR. TEMPLE APPROVED MODIFICATION TO
ADVERSE REACTION SECTION OF LABELING.

29-AUG-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO CONVERSTAION WITH DR. TEMPLE
28-AUG.
CONTACT PERSON: CHEN, SHAW DR. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: DR. CHEN INFORMED OF LABELING ERROR.

29-AUG-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO CONVERSATION WITH DR.
TEMPLE, 28-AUG.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: LABELING CHANGE DISCUSSED.

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29-AUG-91 CONTENT:	51	LETTER RE: FINAL PRINTED LABELING LETTER TO: LIPICKY, RAYMOND M.D. LETTER FROM: MARTIN, IRWIN RE: REFERENCE IS MADE TO PENDING NDA FOR ACCUPRIL (QUINAPRIL HCL) TABLETS, NDA 19-885. ADDITIONAL REFERENCE IS MADE TO OUR SUBMISSION OF DRAFT LABELING (FPL) ON 26-AUG-91 (NDA REF. 48). FURTHER REFERENCE IS MADE TO THE TELEPHONE CONVERSATION BETWEEN DR. ROBERT TEMPLE, OFFICE OF DRUG EVALUATION I, AND THE UNDERSIGNED ON 28-AUG-91 WHEREIN AN ERROR IN FPL WAS DISCUSSED. DR. TEMPLE WAS INFORMED THAT A PROGRAMMING ERROR WAS MADE DURING GENERATION OF THE LISTING OF ADVERSE REACTIONS. THE PARAGRAPH WHICH LISTS "CLINICAL ADVERSE EXPERIENCES PROBABLY OR POSSIBLY RELATED, OR OF UNCERTAIN RELATIONSHIP TO THERAPY OCCURRING IN 0.5% TO 1.0%...OF THE PATIENTS TREATED WITH ACCUPRIL..." ACTUALLY LISTED THESE ADVERSE EXPERIENCES REGARDLESS OF RELATIONSHIP TO THERAPY. CONTINUED - SEE CENTRAL FILE COPY.
30-AUG-91 CONTENT:		FDA CONTACT MEMO MEMO RE: NDA APPROVAL CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: DRAFT "FINAL" LABELING SUBMITTED. DR. TEMPLE OBJECTED TO THE LAUNCH ADVERTISING AND PROMOTION.
30-AUG-91 CONTENT:		FDA CONTACT MEMO MEMO RE: COMPLIANCE REPORT ON MOPS FACILITY AND IMPACT ON NDA APPROVAL. CONTACT PERSON: TEMPLE, R. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: QUINAPRIL NOT APPROVED DUE TO REGULATORY CONCERNS WITH MOPS FACILITY.
30-AUG-91 CONTENT:	52	LETTER RE: LABELING LETTER TO: LIPICKY, RAYMOND LETTER FROM: MARTIN, IRWIN RE: REFERENCE IS MADE TO OUR PENDING NDA FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA 19-885. ADDITIONAL REFERENCE IS MADE TO OUR SUBMISSION OF FINAL PRINTED LABELING ON 26-AUG-91 (NDA REF #48), OUR SUBMISSION ON 29-AUG-91 (NDA RE #51) WHICH CONTAINED CORRECTIONS TO THE ADVERSE REACTIONS SECTION OF THE LABELING, AND TO TELEPHONE CONVERSATIONS WITH MS. KATHLEEN BONGIOVANNI OF YOUR DIVISION ON 27-AUG & 28-AUG-91 IN WHICH MINOR CHANGES TO THE DESCRIPTION AND PRECAUTIONS, HYPERKALEMIA AND POTASSIUM-SPARING DIURETICS SECTIONS OF THE LABELING WERE REQUESTED.

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03-SEP-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: FOLLOW-UP TO FRIDAY NON-APPROVAL. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: MS. BONGIOVANNI UPDATED; FPL REQUESTED.
04-SEP-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: PROVIDE FPL CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: PROVIDE FPL.
04-SEP-91	53	LETTER RE: FINAL PRINTED LABELING
CONTENT:		LETTER TO: LIPICKY, RAYMOND LETTER FROM: MARTIN, IRWIN RE: REFERENCE IS MADE TO OUR PENDING NDA FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA 19-885. WE ARE NOW SUBMITTING FINAL PRINTED LABELING WHICH IS IDENTICAL TO THE TYPESET DRAFT LABELING SUBMITTED ON 30-AUG-91 (REF #52). WE WILL NOT MARKET ACCUPRIL UNTIL WE HAVE RECEIVED WRITTEN APPROVAL. QUESTIONS-----
05-SEP-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS OF WHAT I KNOW OF ACCUPRIL APPROVABILITY. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: MS. BONGIOVANNI UPDATED ON LATEST COMPLIANCE ISSUE. PENDING AMENDMENTS NEED TO BE WITHDRAWN PRIOR TO APPROVAL AND RESUBMITTED AS SUPPLEMENTS.
06-SEP-91		FDA CONTACT MEMO
CONTENT:		MEMO RE: STATUS CHECK. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: NDA UPDATE PROVIDED.

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09-SEP-91 CONTENT:	54	LETTER RE: NDA AMENDMENT - CMC FOR 40 MG TABLETS LETTER TO: LIPICKY, RAYMOND LETTER FROM: BRENNAN, SEAN RE: ENCLOSED IS AN AMENDMENT TO OUR PENDING NDA 19-885 FOR ACCURPIL (QUINAPRIL HYDROCHLORIDE) TABLETS FOR THE MANUFACTURING AND CONTROLS FOR A 40 MG TABLET. ON 31-DEC-90, WE AMENDED THE PENDING NDA TO REMOVE THE 40 MG TABLET DUE TO LACK OF COMMERCIAL INTEREST AT THAT TIME. ON 01-MAY-91, DRS. I. MARTIN AND S. BRENNAN (PARKE-DAVIS) MET WITH DR. R. WOLTERS AND MS. D. CUNNINGHAM (CARDIO-RENAL DIVISION, CDER I) TO DISCUSS A SUPPLEMENT FOR THE 40 MG TABLET. THERE WAS MUTAL AGREEMENT THAT THE SUPPLEMENT FOR THE 40 MG TABLET SHOULD CONTAIN THE FOLLOWING: CONTINUED - SEE FILE COPY.
11-SEP-91 CONTENT:		FDA CONTACT MEMO MEMO RE: UPDATE ON PROMOTIONAL MATERIALS. CONTACT PERSON: FEATHER, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: MEETING DELAYED UNTIL NEW A&P MATERIAL SUBMITTED.
11-SEP-91 CONTENT:		FDA CONTACT MEMO MEMO RE: MUTUAL STATUS UPDATE. CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: MARTIN, I. ABSTRACT: - 40 MG TABLET RECEIVED. - TEMPLE'S OFFICE RECOMMENDS AGAINST GOING OVER THE DISTRICT'S HEAD. - MEETING WITH DRUG ADVERTISING DEPENDENT ON NEW A&P MATERIALS.
13-SEP-91 CONTENT:	55	LETTER RE: FINAL PRINTED LABELING 10/20 MG BLISTER PACKAGE LETTER TO: LIPICKY, RAYMOND LETTER FROM: MARTIN, IRWIN RE: REFERENCE IS MADE TO OUR PENDING NDA FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS, NDA 19-885, SUBMITTED 26-JAN-89. ADDITIONAL REFERENCE IS MADE TO SUBMISSION OF FINAL PRINTED LABELING ON 26-AUG-91 (REF #48) AND TO TELEPHONE CONVERSATIONS WITH MS. K. BONGIOVANNI OF YOUR DIVISION ON 26-AUG 27-AUG-91. AS AGREED IN THE ABOVE-REFERENCED TELEPHONE CONVERSATIONS, WE ARE NOW SUBMITTING FINAL PRINTED LABELS FOR THE 10 MG AND 20 MG UNIT DOSE BLISTER PACKAGES. WE WILL PROVIDE THE BLISTER PACKAGE LABEL FOR THE 5 MG TABLET PRIOR TO MARKETING THE 5 MG UNIT-DOSE PACKAGE.

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CONTENT:

FDA CONTACT MEMO

MEMO RE: NDA UPDATE.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: 40MG REVIEW TO BE COMPLETED SOON.

20-SEP-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: REQUEST PERMISSION TO USE OUR SLIDES
(DRUG NAME DISGUISED) FOR DR. LIPICKY
PRESENTATION OF 24-HOUR BLOOD PRESSURE
DATA.
CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE
MEMO FROM: SPIVEY, R.
ABSTRACT: REQUEST PERMISSION TO USE OUR SLIDES
(DRUG NAME DISGUISED) FOR DR. LIPICKY PRESENTATION
OF 24-HOUR BLOOD PRESSURE DATA.

02-OCT-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA; DELIVER ADVERTISING
MATERIALS.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: 40 MG TO BE APPROVED WITH NDA; A+P
MATERIALS SUBMITTED.

02-OCT-91
CONTENT:

LETTER RE: REVISED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: WITT, ANN
LETTER FROM: MARTIN, I.
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.
FURTHER REFERENCE IS MADE TO OUR PREVIOUS SUBMISS-
ION OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES
VISUAL AID, SUBMITTED ON 26-AUG-91. WE ARE NOW
SUBMITTING THE REVISED VERSION OF BOTH OF THESE
DOCUMENTS FOR YOUR REVIEW. THESE MATERIALS HAVE
ALSO BEEN FORWARDED TO THE DIVISION OF CARDIO-
RENAL DRUG PRODUCTS UNDER SEPARATE COVER.
PLEASE NOTE THAT THE REFERENCES SUBMITTED ON 26-
AUG ALSO SUPPORT THE ENCLOSED MATERIALS.
ADDITIONAL REFERENCES ARE ALSO ATTACHED.
ALSO ENCLOSED IS A COPY OF OUR FINAL PRINTED
LABELING WHICH WAS SUBMITTED ON 04-SEP-91.
I WILL CONTACT YOUR DIVISION TO SCHEDULE A MEETING
TO DISCUSS THE PROPOSED MATERIALS SUBMITTED
HEREIN. QUESTIONS CONTACT ME----

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02-OCT-91 CONTENT:	56	LETTER RE: INITIAL ADVERTISING CAMPAIGN, REVISED MATERIALS LETTER TO: LIPICKY, RAYMOND M.D. LETTER FROM: MARTIN, I. RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885 FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS. REFERENCE IS ALSO MADE TO OUR PREVIOUS SUBMISSION OF PROPOSED ADVERTISING MATERIALS (REF #49, 26-AUG -91). WE HAVE ENCLOSED, FOR YOUR REVIEW, THE REVISED VERSION OF OUR PROPOSED 8-PAGE JOURNAL ADVERTISEMENT AND SALES FORCE VISUAL AID. THESE MATERIALS HAVE ALSO BEEN FORWARDED TO THE DIVISION OF MARKETING, ADVERTISING AND COMMUNICA- TIONS UNDER SEPARATE COVER. PLEASE NOTE THAT THE REFERENCES SUBMITTED ON 26-AUG ALSO SUPPORT THE ENCLOSED MATERIALS. ADDITIONAL REFERENCES ARE ALSO ATTACHED. ALSO ENCLOSED IS A COPY OF OUR FINAL PRINTED LABELING, SUBMITTED ON 04-SEP-91 (REF #53). QUESTIONS CONTACT----
03-OCT-91 CONTENT:		FDA CONTACT MEMO MEMO RE: INFORM FDA OF STATUS OF CHF SUPPLEMENT. CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON MEMO FROM: SPIVEY, R. ABSTRACT: INFORM FDA OF STATUS OF CHF SUPPLEMENT.
04-OCT-91 CONTENT:		FDA CONTACT MEMO MEMO RE: STATUS OF QUINAPRIL A+P REVIEW. CONTACT PERSON: FEATHER, K. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: QUINAPRIL A+P MATERIALS UNDER REVIEW.
04-OCT-91 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO 03-OCT CONVERSATION ON CHF APPLICATION. CONTACT PERSON: BONGIOVANNI, K. VIA TELEPHONE MEMO FROM: SPIVEY, R. DR. PHIL DERN WILL LIKELY BE ASSIGNED TO REVIEW QUINAPRIL CHF DATA.
07-OCT-91 CONTENT:		FDA CONTACT MEMO MEMO RE: FOLLOW-UP TO CONVERSATION WITH MR. FEATHER, 04-OCT-91. CONTACT PERSON: CHURNEY, I. VIA TELEPHONE MEMO FROM: MARTIN, I. ABSTRACT: ACCUPRIL A+P MATERIALS TO BE REVISED AGAIN PRIOR TO FDA MEETING.

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09-OCT-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF ADVERTISING REVIEW LETTER.
CONTACT PERSON: CERNY, I. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: REVIEW LETTER RECEIVED.

09-OCT-91
CONTENT:

LETTER RE: RESPONSE TO LAUNCH MATERIALS

LETTER TO: MARTIN, I.
LETTER FROM: CERNY, IGOR
RE: THIS LETTER IS IN RESPONSE TO YOUR ACCUPRIL
LAUNCH MATERIALS SUBMITTED 26-AUG-91 AND REVISED
MATERIALS SUBMITTED 02-OCT-91. BOTH THE JOURNAL
AD (PD-103-JA-6112-A1) AND THE SALES VISUAL (PD-
103-VA-6856-A1) CONTAIN NUMEROUS MISLEADING AREAS.
THESE CONCERNS ARE OUTLINED BELOW THEMATICALLY:
1) TISSUE ACE INHIBITION CLAIM : SEE FILE COPY.
2) THE "REDUCE BLOOD PRESSURE SINGLE-HANDEDLY"
CLAIM: SEE FILE COPY.
3) MISCELLANEOUS: SEE FILE COPY.
THIS LIST SHOULD NOT BE CONSIDERED EXHAUSTIVE AND
WE SUGGEST THAT IN SUBSEQUENT SUBMISSIONS, THE
LABELING OF THE PRODUCT IS STRICTLY ADHERED TO.
AT THIS TIME A MEETING WOULD SEEM COUNTERPRO-
DUCTIVE SINCE THE LAUNCH CAMPAIGN NEEDS MAJOR
REVISION. WE AWAIT YOUR RESUBMISSION OF A REVISED
PIECE.

18-OCT-91
CONTENT:

LETTER RE: REVISED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: WITT, ANNA
LETTER FROM: MARTIN, IRWIN
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.
FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS
OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES
VISUAL AID, SUBMITTED ON 26-AUG AND 02-OCT, AND TO
AN 09-OCT-91 LETTER FROM DR. IGOR CERNY OF YOUR
DIVISION. WE ARE NOW SUBMITTING REVISED MATERIALS
IN RESPONSE TO THE ABOVE-REFERENCED LETTER AND
BELIEVE WE HAVE ADDRESSED THE STATED CONCERNS.
HOWEVER, CONSISTENT WITH COMMON INDUSTRY PRACTICE,
WE HAVE CONTINUED TO INCLUDE ONLY THE STARTING
DOSE, 10 MG, IN ASSOCIATION WITH THE ACCUPRIL NAME
ON THE COVER PAGE. PURSUANT TO 21 CFR 202.1(D) (2),
WE BELIVE ONE TABLET STRENGTH NEEDS TO BE
MENTIONED IN THE ADVERTISEMENT.
CONTINUED - SEE FILE COPY.

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18-OCT-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: DELIVER REVISED A+P MATERIAL.
CONTACT PERSON: CERNY, I. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: REVISED A+P LAUNCH MATERIALS PROVIDED.

18-OCT-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: DELIVER DESK COPIES AND UPDATE STATUS.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: APPROVAL LETTER TO BE UPDATED WITH NEW SUBMISSIONS.

18-OCT-91 FDA CONTACT MEMO

CONTENT:

MEMO RE: REQUEST FOR 10/24 ADVISORY COMMITTEE MEETING.
CONTACT PERSON: CHEN, S. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: KEY TO 'BESTAPRIL' SLIDES REQUESTED.

18-OCT-91
CONTENT:

57 LETTER RE: FINAL PRINTED LABELING 40 MG BLISTER PACKAGE

LETTER TO: LIPICKY, RAYMOND MD
LETTER FROM: MARTIN, IRWIN
RE: REFERENCE IS MADE TO OUR PENDING NDA FOR ACCUPRIL (QUINAPRIL/HYDROCHLORIDE) TABLETS, NDA 19-885, SUBMITTED 26-JAN-89. FURTHER REFERENCE IS MADE TO OUR AMENDMENT (REF #54, 09-SEP-91) TO INCLUDE MANUFACTURING AND CONTROLS FOR A 40 MG TABLET.
WE ARE NOW SUBMITTING FINAL PRINTED LABELS FOR THE 40 MG UNIT DOSE BLISTER PACKAGES.
QUESTION CALL-----

18-OCT-91
CONTENT:

58 LETTER RE: REVISED JOURNAL ADVERTISEMENT & SALES VISUAL AID

LETTER TO: LIPICKY, RAYMOND
LETTER FROM: MARTIN, IRWIN
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885 FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS. FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES VISUAL AID, SUBMITTED ON 26-AUG AND 02-OCT, AND TO AN 09-OCT-91 LETTER FROM DR. IGOR CERNY OF THE DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS. WE ARE NOW SUBMITTING REVISED MATERIALS IN RESPONSE TO THE ABOVE-REFERENCED LETTER AND BELIEVE WE HAVE ADDRESSED THE STATED CONCERNS. HOWEVER, CONSISTENT WITH COMMON INDUSTRY PRACTICE, WE HAVE CONTINUED TO INCLUDE ONLY THE STARTING DOSE, 10 MG, IN ASSOCIATION WITH THE ACCUPRIL NAME ON THE COVER PAGE. PURSUANT TO

21 CFR 202.1(D) (2), WE BELIEVE ONE TABLET STRENGTH
NEEDS TO BE MENTIONED IN THE ADVERTISEMENT.
CONTINUED - SEE FILE COPY.

REGULATORY LIAISON AND COMPLIANCE
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21-OCT-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: PROVIDE INFORMATION ON CODING SCHEMES
USED FOR "BESTAPRIL" SLIDES FOR CARDIO-
RENAL ADVISORY COMMITTEE MEETING.
CONTACT PERSON: CHEN, S. VIA TELEPHONE
MEMO FROM: SPIVEY, R.
ABSTRACT: PROVIDE INFORMATION ON CODING SCHEMES
USED FOR "BESTAPRIL" SLIDES FOR CARDIO RENAL
ADVISORY COMMITTEE MEETING; 03-OCT.

23-OCT-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: STATUS OF A+P REVIEW (10/18 SUBMISSION).
CONTACT PERSON: CERNY, I. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: RECENT SUBMISSION OF A+P MATERIALS STILL
NEED REVISION.

24-OCT-91 LETTER RE: LAUNCH PROMOTIONAL MATERIALS
CONTENT:

LETTER TO: SMITH, JOSEPH
LETTER FROM: CERNY, IGOR
RE: THIS IS IN REFERENCE TO LAUNCH PROMOTIONAL
MATERIALS FOR ACCUPRIL SUBMITTED TO US ON 18-OCT-
91 IDENTIFIED AS PD-103-JA-6112-A1 AND PD-103-VA-
6856-A1.
YOUR 18-OCT-91 SUBMISSION REPRESENTS THE SECOND
REVISION OF THESE LAUNCH MATERIALS. HOWEVER, YOUR
THIRD BATCH OF LAUNCH MATERIALS CONTAINS NEARLY
IDENTICAL FALSE AND MISLEADING ITEMS WHICH WERE
OBJECTED TO INITIALLY. OUR 09-OCT-91 LETTER TO
I. MARTIN, CLEARLY OUTLINES THE AREAS OF THE
PROMOTIONAL PIECES WHICH WE FIND OBJECTIONABLE.
FOR YOUR CONVINIENCE, THESE OBJECTIONABLE AREAS
ARE REITERATED BELOW.
CONTINUED - SEE FILE COPY.

29-OCT-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP TO 23-OCT CONTACT RE: MEETING
REQUEST.
CONTACT PERSON: CERNY, I. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: NEW LETTER SENT ON A+P MATERIALS.

29-OCT-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: FOLLOW-UP ON 24-OCT LETTER TO J. SMITH
RE: LAUNCH MATERIALS.
CONTACT PERSON: FEATHER, K. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: FRUSTRATION OVER 24-OCT LETTER VENTED.

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29-OCT-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: GET MEETING DATE PREFERENCES.
CONTACT PERSON: CERNY, I. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: BACKGROUND PACKAGE TO BE PROPOSED FOR
ADVISORY MEETING.

30-OCT-91 FDA CONTACT MEMO
CONTENT:

MEMO RE: MEETING DATE FOR ADVERTISING REVIEW
MEETING.
CONTACT PERSON: CERNY, I. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: MEETING DATE STILL NEEDED.

04-NOV-91 LETTER RE: PROPOSED JOURNAL ADVERTISEMENT & SALES VISUAL AID
CONTENT:

LETTER TO: WITT, ANN
LETTER FROM: MARTIN, I.
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.
FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS
OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES
VISUAL AID, SUBMITTED ON 26-AUG, 02-OCT, AND
18-OCT-91. ADDITIONAL REFERENCE IS MADE TO 09-OCT
AND 24-OCT LETTER FROM DR. IGOR CERNY OF YOUR
DIVISION.
IN THE 24-OCT LETTER DR. CERNY STATES THAT OUR
REVISED MATERIALS "CONTAIN NEARLY IDENTICAL FALSE
AND MISLEADING ITEMS AS WERE OBJECTED TO
INITIALLY." WE BELIEVE WE ADDRESSED THESE
COMMENTS. REVIEWED BELOW ARE THE INITIAL
OBJECTIONS AND OUR COMMENTS.
CONTINUED - SEE FILE COPY.

04-NOV-91 59 LETTER RE: PROPOSED JOURNAL ADVERTISEMENT & SALES VISUAL AID
CONTENT:

LETTER TO: LIPICKY, RAYMOND M.D.
LETTER FROM: MARTIN, IRWIN
RE: REFERENCE IS MADE TO OUR PENDING NDA 19-885
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) TABLETS.
FURTHER REFERENCE IS MADE TO PREVIOUS SUBMISSIONS
OF OUR PROPOSED JOURNAL ADVERTISEMENT AND SALES
VISUAL AID, SUBMITTED ON 26-AUG, 02-OCT, AND
18-OCT-91. ADDITIONAL REFERENCE IS MADE TO 09-OCT
AND 24-OCT LETTERS FROM DR. IGOR CERNY, DIVISION
OF MARKETING, ADVERTISING AND COMMUNICATIONS.
IN THE 24-OCT LETTER DR. CERNY STATES THAT OUR
REVISED MATERIALS "CONTAIN NEARLY IDENTICAL FALSE
AND MISLEADING ITEMS AS WERE OBJECTED TO
INITIALLY." WE BELIEVE WE ADDRESSED THESE
COMMENTS. REVIEWED BELOW ARE THE INITIAL
OBJECTIONS AND OUR COMMENTS.
CONTINUED - SEE FILE COPY.

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DOC DATE SER/SUPPL NO TITLE

05-NOV-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: PROVIDE DESK COPIES; UPDATE NDA STATUS.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: NDA WILL BE APPROVED FOR 36 MONTH
EXPIRATION DATING. STATUS OF APPROVAL AND FUTURE
LABELING CHANGES DISCUSSED. ACCURETIC MAY HAVE
1991 APPROVABLE STATUS.

06-NOV-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF MOPS INSPECTION.
CONTACT PERSON: WOLTERS, R. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: DR. WOLTERS TO BE CALLED UPON MOPS
APPROVAL.

13-NOV-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF INSPECTION.
CONTACT PERSON: BONGIOVANNI, K. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: UPDATED STATUS OF MOPS AND HOLLAND
INSPECTIONS.

13-NOV-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: CLARIFY 19-NOV MEETING ATTENDEES.
CONTACT PERSON: CERNY, I. VIA IN PERSON
MEMO FROM: MARTIN, I.
ABSTRACT: ATTENDEES CLARIFIED.

15-NOV-91
CONTENT:

FDA CONTACT MEMO

MEMO RE: STATUS OF NDA APPROVAL LETTER.
CONTACT PERSON: CARTER, L. VIA TELEPHONE
MEMO FROM: MARTIN, I.
ABSTRACT: APPROVAL EXPECTED 18-NOV.

19-NOV-91
CONTENT:

LETTER RE: APPLICATION APPROVED EFFECTIVE

LETTER TO: MARTIN, IRWIN
LETTER FROM: TEMPLE, ROBERT
RE: PLEASE REFER TO YOUR 26-JAN-91 NDA SUBMITTED
FOR ACCUPRIL (QUINAPRIL HYDROCHLORIDE) 5, 10, 20,
AND 40 MG TABLETS.
WE ALSO ACKNOWLEDGE RECEIPT OF YOUR AMENDMENTS AND
CORRESPONDENCE DATED 23 & 24-MAY, 20, 21, 22,
26 (TWO), 29, & 30-AUG, 04, 09, & 13-SEP, 02 AND
18 (TWO)-OCT AND 04-NOV-91.
WE HAVE COMPLETED THE REVIEW OF THIS APPLICATION
AND HAVE CONCLUDED THAT ADEQUATE INFORMATION HAS
BEEN PRESENTED TO DEMONSTRATE THAT THE DRUG IS

SAFE AND EFFECTIVE FOR USE AS RECOMMENDED IN THE
FINAL PRINTED LABELING SUBMITTED 09-SEP-91
(PACKAGE INSERT) AND 26-AUG, 09 & 16-SEP, AND
18-OCT-91 (CARTON AND CONTAINER LABELS).
ACCORDINGLY, THE APPLICATION IS APPROVED EFFECTIVE
ON THE DATE OF THIS LETTER.
CONTINUED - SEE FILE COPY.